Southern Medical Journal

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AUGUST, 1956 Volume 49 Number 8

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AUGUST 1956

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2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
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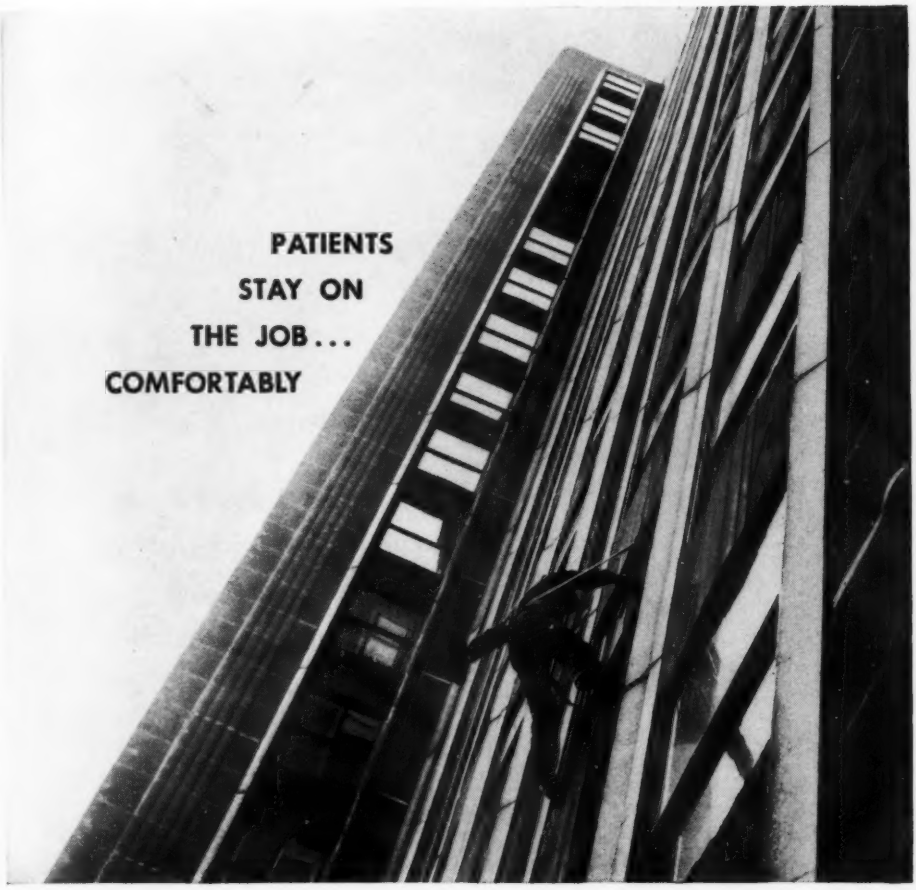

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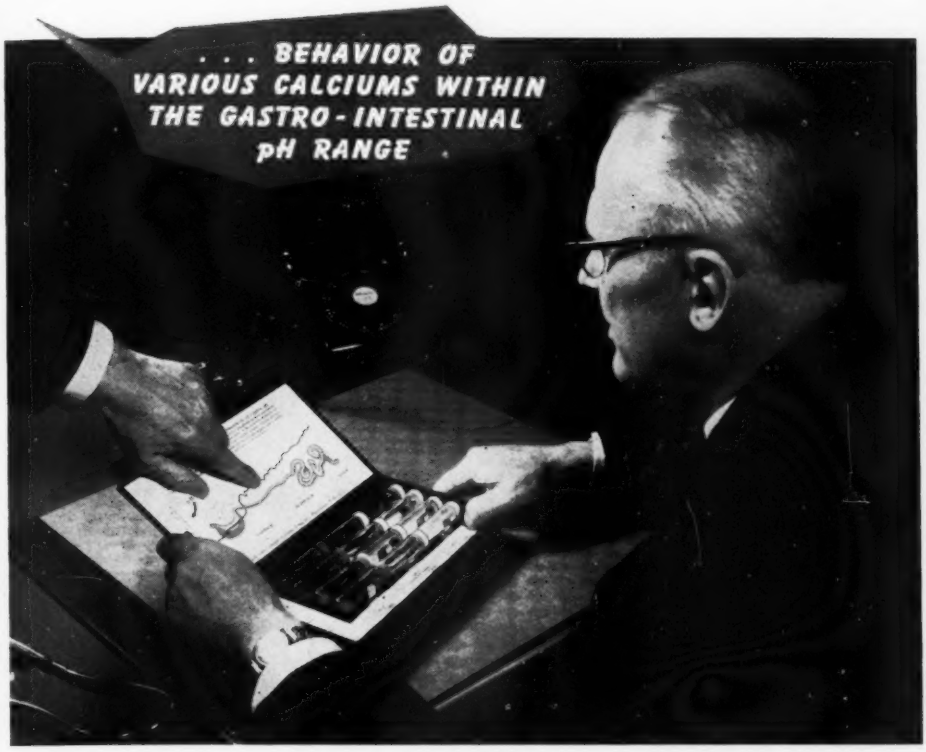

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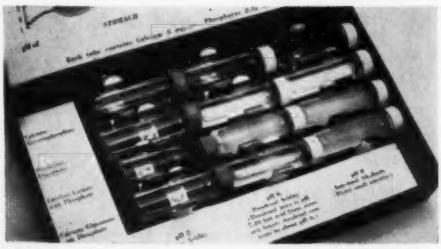

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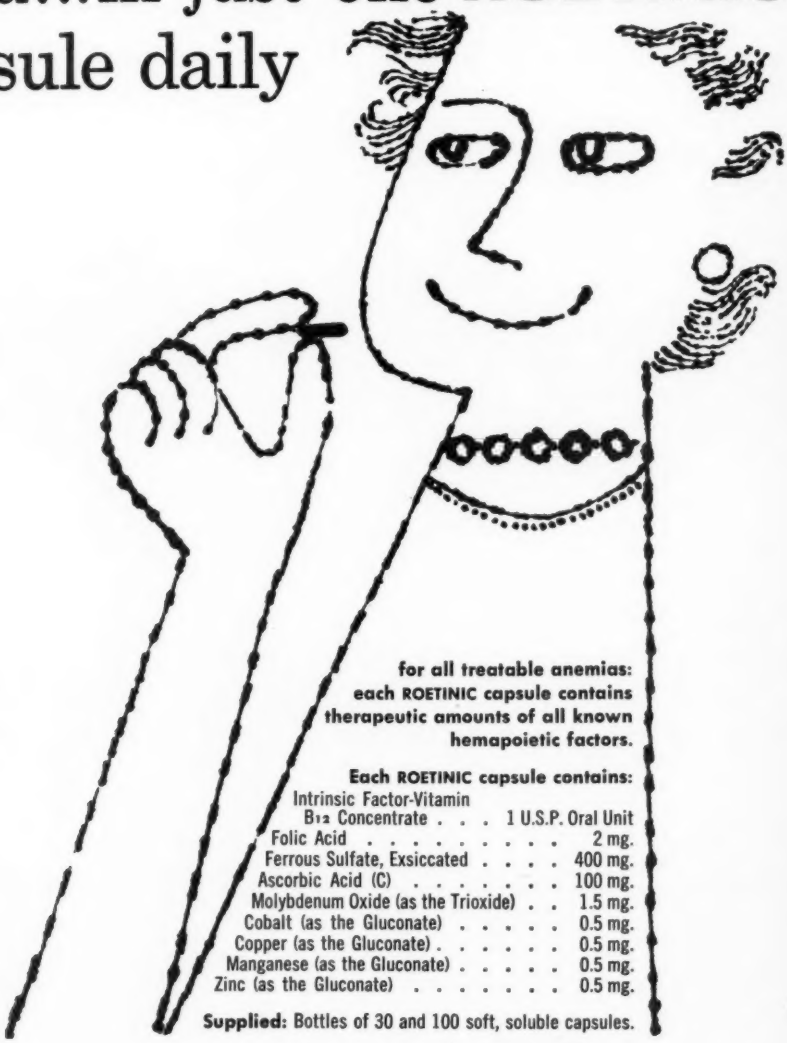

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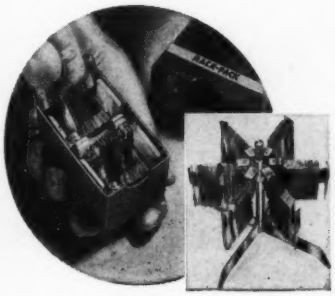

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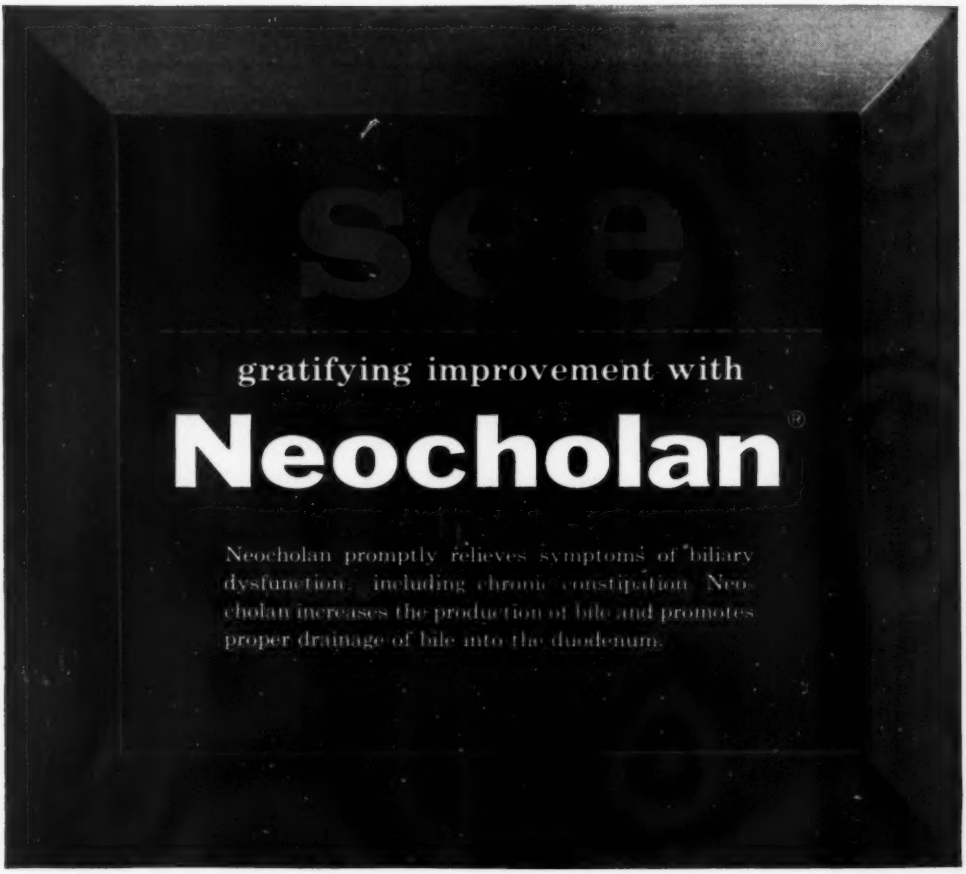
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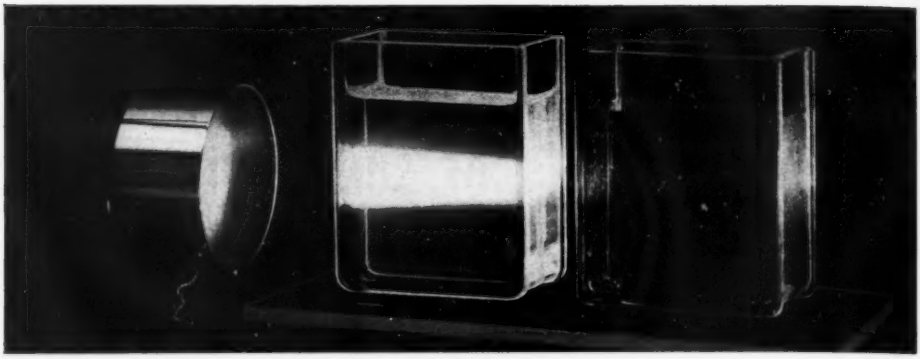

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Bibliography: 1. West, E. S., and Todd, W. R.: Textbook of Biochemistry, New York, The Macmillan Company, 1952, p. 184. • 2. Drill, V. A.: Pharmacology in Medicine, New York, McGraw-Hill Book Company, Inc., 1954, p. 64/6. • 3. Ahrens, E. H., Jr., and Kunkel, H. G.: J. Exper. Med. *90*:409 (Nov. 1) 1949.

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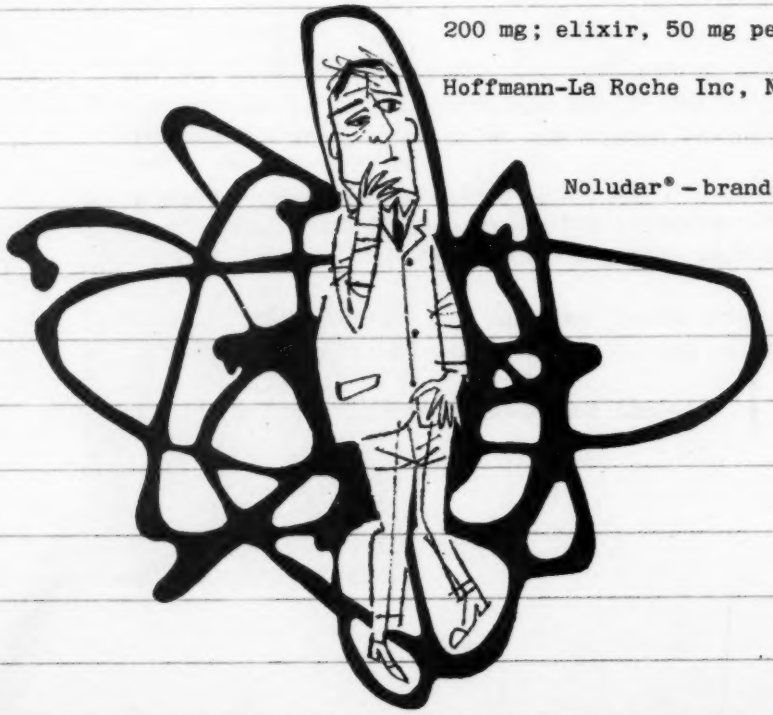

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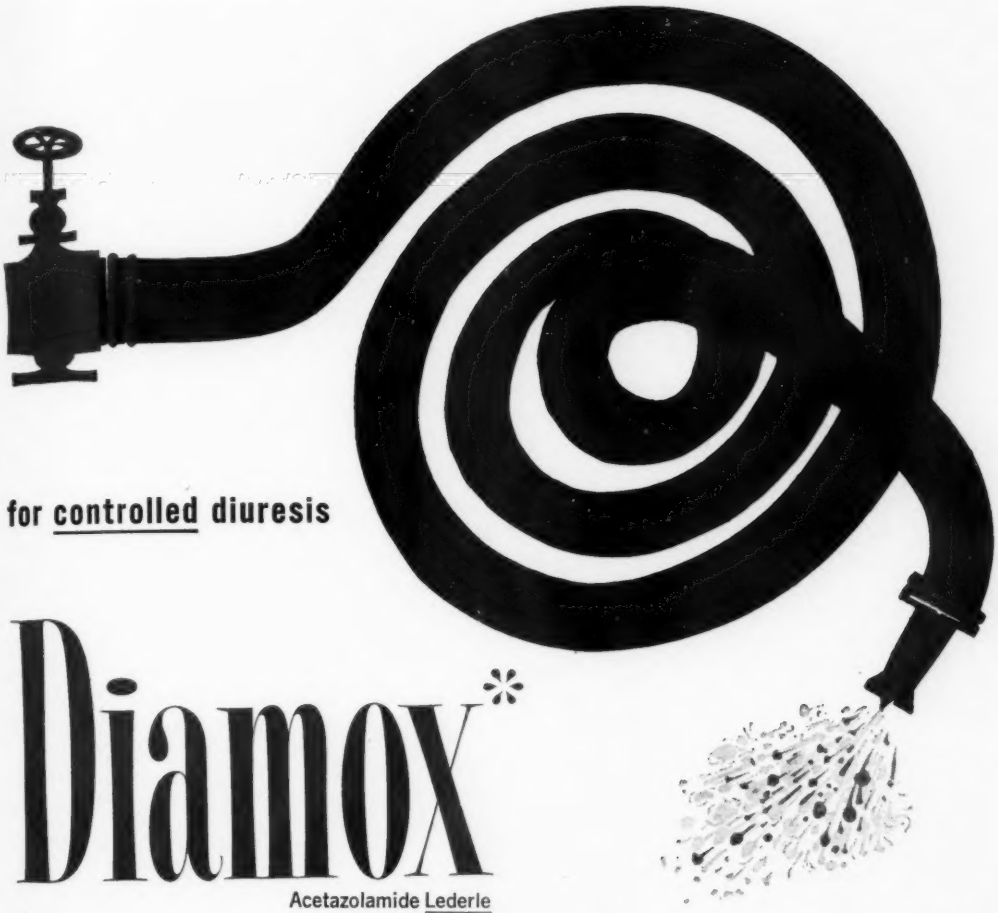

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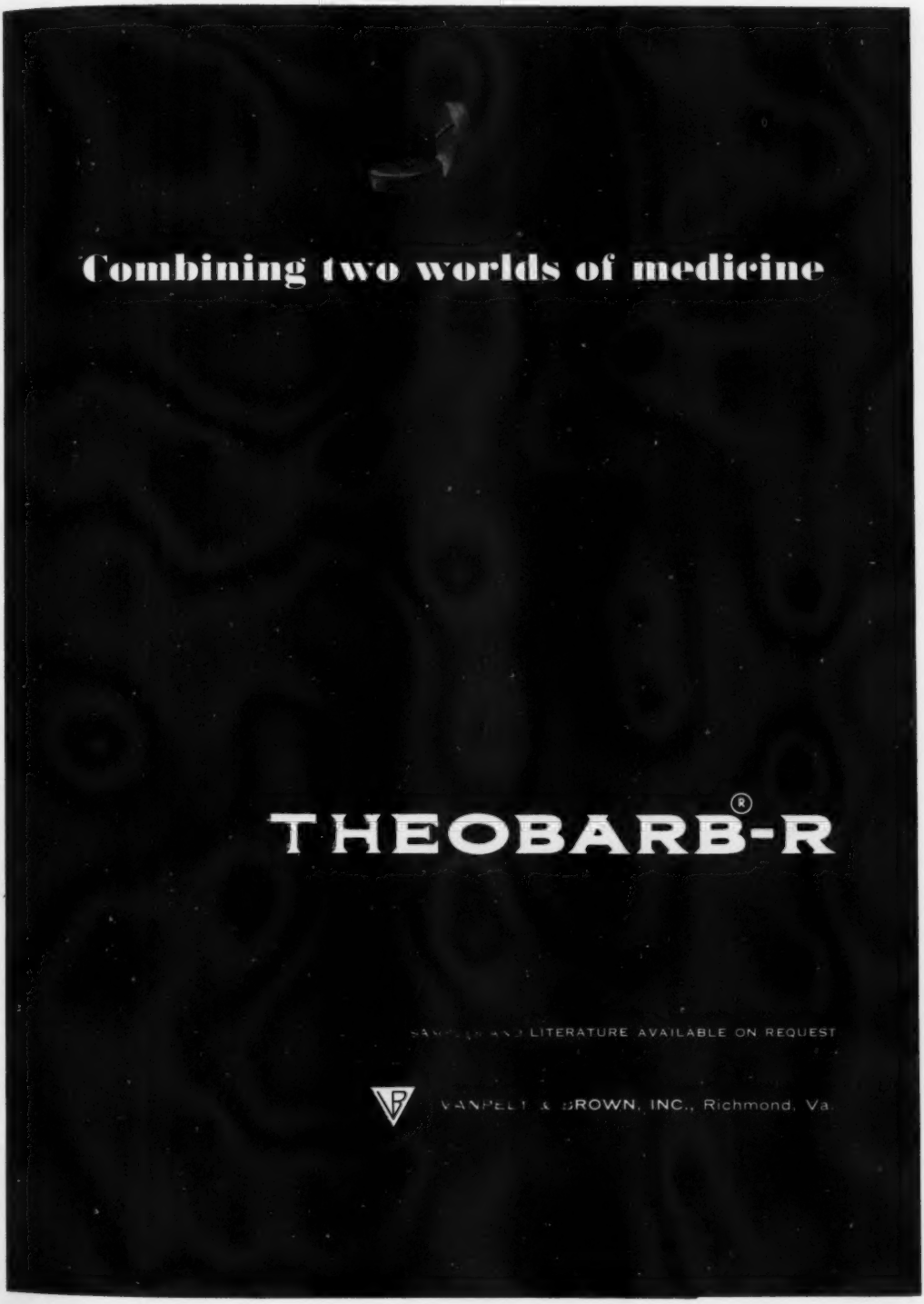
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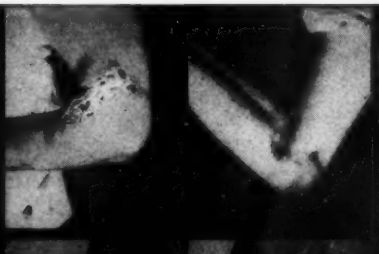
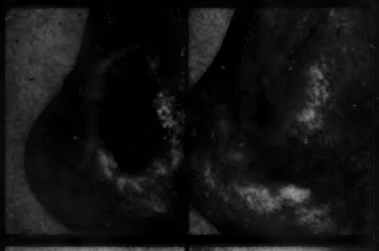


left
Traumatic ulceration with edema in a paralyzed arm

right
Almost complete healing with Panthoderm Cream applied twice daily for three weeks

relieves
pain
and itching...
stimulates
healing

even
when
other
therapy
fails...



left
Varicose ulcer of ankle, large, deep, profuse foul-smelling discharge

right
Healing of ulcer after treatment with Panthoderm Cream for ten weeks

left
Gangrenous ulcer of the buttocks

right
Healing after twice daily application of Panthoderm Cream for four weeks

left
Diabetic ulceration of great toe of two months' duration, unresponsive to previous therapy

right
Complete healing after two weeks therapy with Panthoderm Cream

panthoderm cream

2% Pantothenylol (analog of pantothenic acid) in a water-miscible base

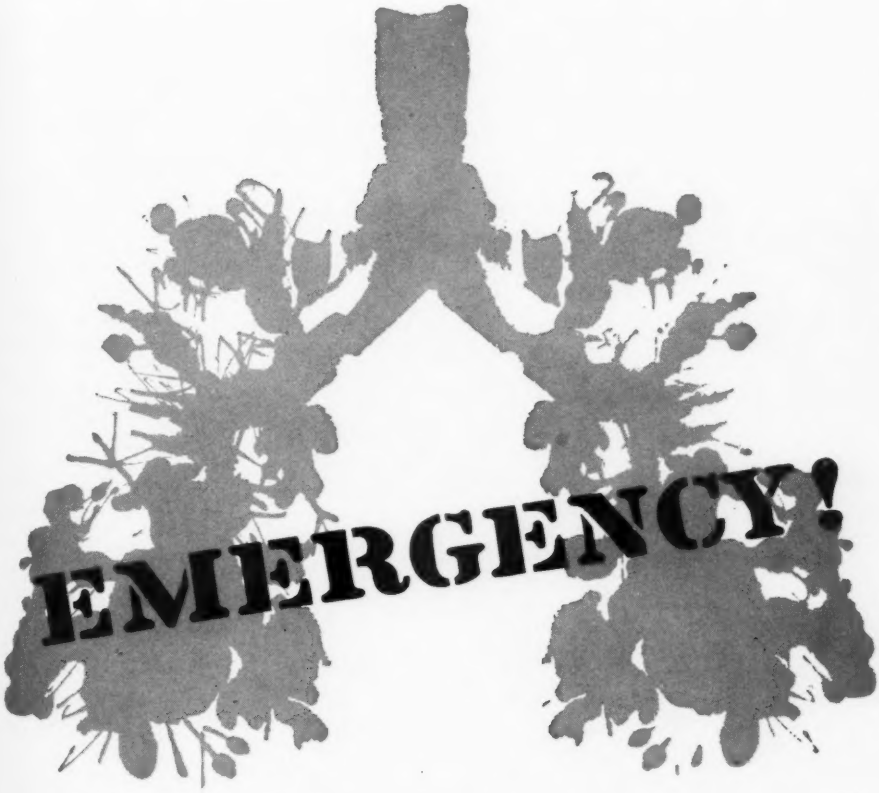
non-sensitizing
aesthetically agreeable

available in 1 oz. tubes; 2 oz. and 1 lb. jars

SAMPLES and literature available upon request

u. s. vitamin corporation

Arlington-Funk Laboratories, division 250 East 43rd Street • New York 17, N.Y.



in severe asthma

THORAZINE*

is highly effective—
and often lifesaving[1]

1. Ende, M.: Am. Pract. & Dig. Treat. 6:710 (May) 1955.

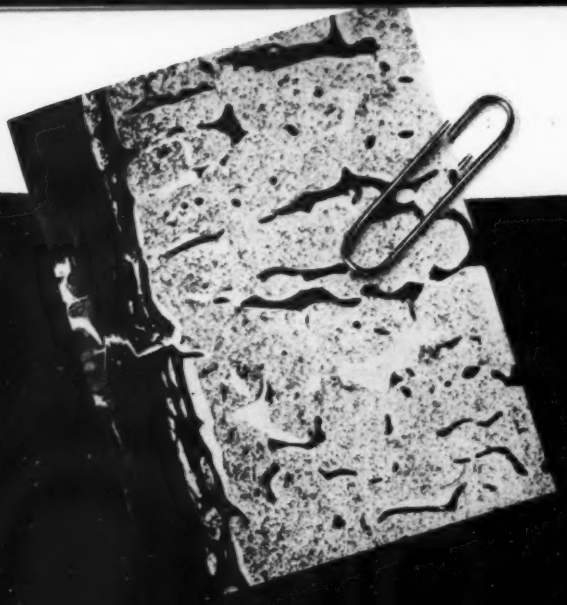
Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

'Thorazine' is available in ampuls, tablets and syrup as the hydrochloride; and in suppositories as the base.

'Thorazine' should be administered discriminately and, before prescribing, the physician should be fully conversant with the available literature.

always carry 'Thorazine' Ampuls in your bag



GYNETONE REPETABS

for osteopo

Combined estrogen-

therapy with GYNETONE

stimulates prote

to improve bone-buildi

and to enhance

redeposition with minim

effects of either

when bones begin
to show signs
change

*Reifenstein, E. C., Jr., and Albright, F.: J. Clin. Investigation *26*:24, 1947.

for individualized therapy: two strengths

GYNETONE REPETABS ".02": Ethinyl Estradiol U.S.P. 0.02 mg. plus 5 mg. Methyltestosterone U.S.P.
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GYNETONE,® combined estrogen-androgen.
REPETABS,® Repeat Action Tablets. 67-63-256

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unchanged life

in the changing years

two strengths

0.02 mg. ethinyl estradiol plus 5 mg. Methyltestosterone U.S.P.
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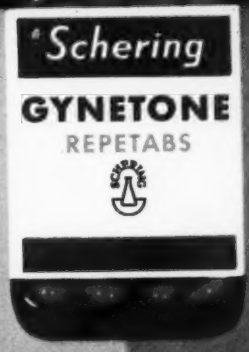
GYNETONE,® combined estrogen-androgen.
REPETABS,® Repeat Action Tablets. GT-J-61-255



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for therapeutic
convenience

daylong relief from a single dose

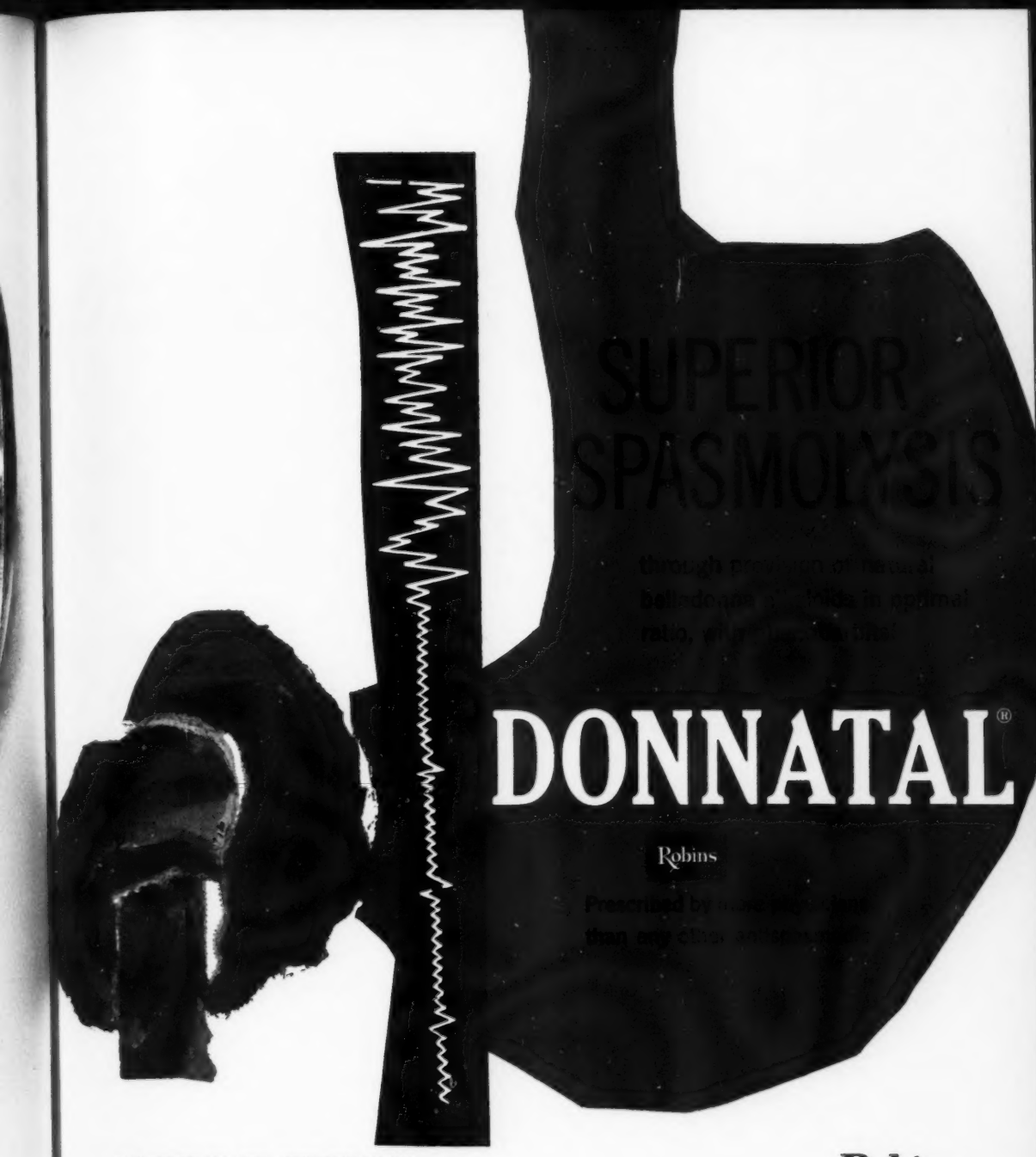
CHLOR-TRIMETON REPETABS 8 and 12 mg.

PRANTAL REPETABS 100 mg.

GYNETONE REPETABS ".02" and ".04"

CHLOR-TRIMETON® Maleate, brand of chlorprophenpyridamine maleate.
PRANTAL® Methylsulfate, brand of diphemanil methylsulfate.
GYNETONE,® combined estrogen-androgen.
REPETABS,® Repeat Action Tablets.

M-J-62-388



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Ethical Pharmaceuticals of Merit since 1878

Robins

FORMULA

Donnatal Tablets
Donnatal Capsules
Donnatal Elixir (per 5 cc.)

Hyoscyamine Sulfate . .	0.1037 mg.
Atropine Sulfate	0.0194 mg.
Hyoscine Hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.) . . .	16.2 mg.

DONNATAL® EXTENTABS®
(Extended Action Tablets)

Each Extentab (equivalent to 3 Tablets) provides sustained 1-tablet effects . . . evenly, for 10 to 12 hours—all day or all night on a single dose.

Also available without phenobarbital component, as **Donna® Extentabs®.**

Combined for a new attack on resistant

new

METRETON *tablets*

METICORTEN (PREDNISONE) PLUS CHLOR-TRIMETON WITH ASCORBIC ACID

For prompt and effective relief, especially in many resistant allergic disorders, METRETON affords the benefits of two established agents with unexcelled anti-inflammatory, anti-allergic and antipruritic effectiveness. ***supported by essential vitamin C***—for stress support and for postulated effect on prolonging steroid action ***no better corticosteroid***—original brand of prednisone...minimal electrolyte effects—METICORTEN ***no better antihistamine***—unexcelled in potency and freedom from side effects—CHLOR-TRIMETON effective against hay fever, pollen asthma, perennial rhinitis, acute and chronic urticaria, angioneurotic edema, drug reactions, inflammatory and allergic eye disorders, pruritic and contact dermatoses.

formula: Each tablet of METRETON provides 2.5 mg. of METICORTEN (prednisone), 2 mg. of CHLOR-TRIMETON maleate (chlorprophenpyridamine maleate), and 75 mg. ascorbic acid.

supplied: METRETON Tablets, bottles of 30 and 100.

frontal attack allergies

new

METRETON nasal spray

METICORTELONE (PREDNISOLONE) PLUS CHLOR-TRIMETON

quickly clears nasal passages • avoids rebound engorgement and sympathomimetic side effects • safe even for cardiacs, hypertensives, children, pregnant patients •

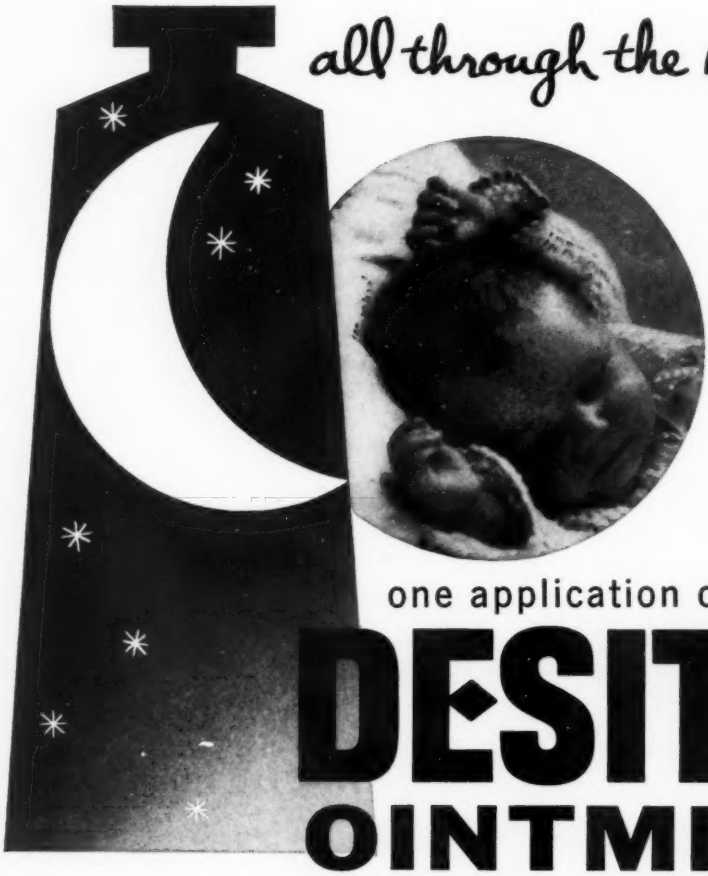
Composition: Contains 2 mg. (0.2%) METICORTELONE acetate (prednisolone acetate) and 3 mg. (0.3%) of CHLOR-TRIMETON gluconate (chlorprophenpyridamine gluconate) in each cc.

Packaging: 15 cc. plastic "squeeze" bottle, box of 1.

METRETON,* brand of corticoid-antihistamine compound; METICORTEN,* brand of prednisone; METICORTELONE,® brand of prednisolone; CHLOR-TRIMETON,® brand of chlorprophenpyridamine preparations. *T.M.

MT-J-876

Schering



all through the night

one application of

DESITIN® OINTMENT

helps protect the infant's skin against

diaper rash (ammoniacal dermatitis) • **irritation** • **excoriation**

DESITIN OINTMENT covers the infant's skin with a soothing, protective, healing coating which is largely impervious to and helps guard against irritation, rash, and maceration caused by urine, excrement, perspiration and secretions. This preventive action of Desitin Ointment *persists all through the night*...when baby is particularly vulnerable to painful skin excoriations.

Nonsensitizing, nonirritant Desitin Ointment..**rich in cod liver oil** ....successfully used on millions of infants for over 30 years.

- tubes of 1 oz., 2 oz., 4 oz.
- 1 lb. jars.

for **samples** *and literature please write....*

DESITIN CHEMICAL COMPANY 70 Ship Street Providence 2, R. I.

1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. Med. 53:2233, 1953. **2.** Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951. **3.** Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949. **4.** Turell, R.: New York St. J. Med. 50:2282, 1950. **5.** Marks, M. M.: Missouri Med. 52:187, 1955.

In Congestive Heart Failure
R_x 'Wide Safety Margin'
GITALIGIN®

WHITE'S BRAND OF AMORPHOUS GITALIN

Authoritative investigators have reported that the digitalizing dose of Gitaligin is approximately one-third the toxic dose.[1-5]

This "wide margin of safety" (difference between therapeutic and toxic doses) permits rapid digitalization and successful maintenance with a minimum of toxic side reactions—even in refractory cases where other glycosides have failed.[6] And, cost to your patient is no greater than ordinary digitalis preparations.

Supplied: Scored tablets of 0.5 mg. Bottles of 30 and 100.

References: 1. Ehrlich, J. C.: Arizona Med. *12:* 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. *227:* 188 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. *39:* 1189 (Dec.) 1953. 4. Hejtmancik, M. R., and Herrmann, G. R.: Texas St. J. M. *51:* 238 (May) 1955. 5. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation *5:* 201 (Feb.) 1952. 6. Denham, R. M.: J. Kentucky St. M. Assoc. *53:* 209 (Mar.) 1955.

It's so easy to switch to 'wide safety margin' Gitaligin. Follow these simple dosage equivalents wherever digitalis therapy is indicated:

DIGITALIS PREPARATION	AVERAGE DAILY MAINTENANCE DOSE	GITALIGIN DOSAGE EQUIVALENT (APPROX.)
Digitalis leaf	0.1 Gm.	0.5 mg.
Digitoxin	0.1 mg.	0.5 mg.
Digoxin	0.5 mg.	0.5 mg.

WHITE LABORATORIES, INC. Kenilworth, N. J.

UNITENSEN-R

a combination ideally suited for treating moderate to severe hypertension where blood pressure has to be lowered

UNITENSEN + RESERPINE = UNITENSEN-R

ADVANTAGES	ADVANTAGES	COMBINES THE ADVANTAGES OF EACH ELIMINATES THE DISADVANTAGES OF BOTH
positive, dependable lowering of blood pressure	mild, hypotensive action	easier to prescribe because of the single dosage form
safety... no postural hypotension, bladder obstruction or renal complication	calming... tranquilizing effects	dependably lowers blood pressure
improvement of total circulation and increased cardiac efficiency	safety	economical
economy	well tolerated in average doses	the component drugs "acting in concert"[1] cut dosage requirements in half... practically eliminating side reactions
DISADVANTAGES	**DISADVANTAGES**	therapy with complete safety
nausea and emesis in higher dosage	slow acting	
some flatulence, nervousness and urinary frequency	not effective alone in moderate and severe hypertension	
	may cause nasal stuffiness, weight gain... depression in some patients	

1. Cohen, B.M.; Cross, E.B., and Johnson, W.: Am. Pract. 6: 1030, 1955.

UNITENSEN*-R

also available: **UNITENSEN*** tannate tablets
(contain cryptenamine 2 mg.)

TO SERVE YOUR PATIENTS TODAY—Call your pharmacist for any additional information you may need to help you prescribe Unitensen-R. He has been especially alerted.

Each tablet contains:

Cryptenamine 1 mg.
(as the tannate salt)
Reserpine 0.1 mg.

For prescription economy: prescribe Unitensen-R in 50's

1 tablet t.i.d.

*T.M., Reg. U.S. Pat. Off.

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

In answer to questions about douching you can recommend META CINE with complete confidence

BECAUSE META CINE:

1. is a safe, soothing douche (pH 3.5) containing methyl salicylate, eucalyptol, menthol, chlorothymol and PAPAIN to liquefy mucus. CITRIC ACID to help restore the proper acid pH, discourage pathogenic organism, promote normal vaginal flora. LACTOSE to feed the physiologic Doderlein bacilli.

2. is pleasant and refreshing to the patient . . . and deodorizing.

3. has a surface tension of 56 dynes/cm as compared to 72 dynes/cm for the usual vinegar douche.

4. is economical . . . only two teaspoonfuls to two quarts of water . . . supplied in eight-ounce containers.

5. is useful as a routine, cleansing douche, as an adjuvant when treating leukorrheal infections, and following cervical cauterizations and conizations.

UPON YOUR REQUEST *a free supply of instruction sheets will be sent for your convenience in advising patients on the correct douching technique.*

BRAYTEN PHARMACEUTICAL COMPANY, 3810 St. Elmo Avenue, Chattanooga 9, Tennessee

"home is the hunter"

... with dermatitis

anti-infective
anti-inflammatory

indicated: **Terra-Cortril®**

brand of oxytetracycline and hydrocortisone

TOPICAL OINTMENT

For the profusion of dermatoses that come with summer, TERRA-CORTRIL provides the outstanding action of two proved agents — anti-infective TERRAMYCIN® and anti-inflammatory CORTRIL.® Whether of allergic or traumatic origin with their frequent infectious complications, or of bacterial etiology with the usual inflammatory symptoms, TERRA-CORTRIL effects comprehensive control for rapid relief and involution.

supplied: In 1/2-oz. tubes, containing 3% oxytetracycline hydrochloride (TERRAMYCIN) and 1% hydrocortisone (CORTRIL).

also available: TERRA-CORTRIL Ophthalmic Suspension.

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

SATISFACTORY REMISSION OF

SYMPTOMS WITHOUT SIGNIFICANT

SIDE EFFECTS REPORTED IN

85% OF RHEUMATIC PATIENTS

TREATED IN CLINICAL TESTS

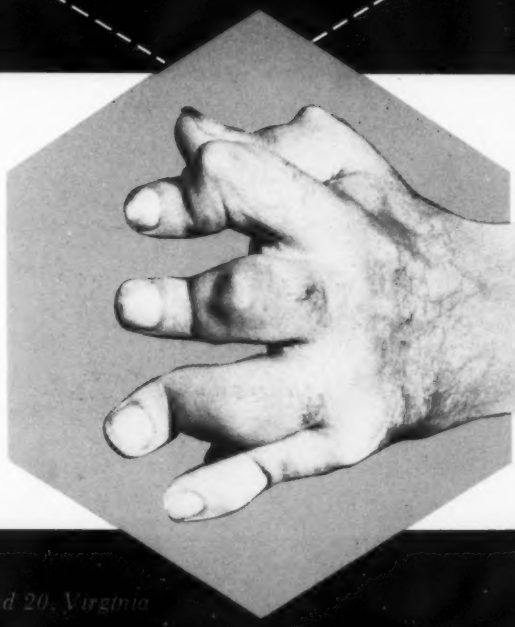
PABALATE-HC

PABALATE WITH HYDROCORTISONE

Robins

The *complete*, rational formula for

- *full* hormone effects on low hormone dosage
- with a much higher degree of *safety*
- even when therapy is *prolonged*
- at significant *economy* for the patient
- *enteric coating* precludes gastric irritation



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A. H. ROBINS CO., INC., *Richmond 20, Virginia*

In each enteric-coated tablet

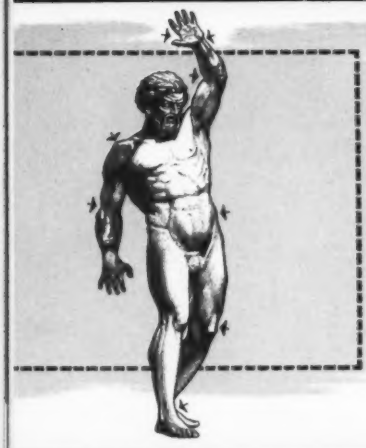
Hydrocortisone (alcohol)	2.5 mg.
Potassium salicylate (5 gr.)	0.3 Gm.
Potassium para-aminobenzoate (5 gr.)	0.3 Gm.
Ascorbic acid	50.0 mg.

Dosage: 2 tablets, q.i.d.; or as required

FOR SALICYLATE (NON-STEROID) THERAPY, SEE OVER

Published reports* confirm:
More effective than salicylate alone, for the conservative therapy of rheumatic affections

PABALATE® or PABALATE-SODIUM FREE



Each of these double-antirheumatic formulae, through synergism, insures—

- **prompt symptomatic relief**
- **for prolonged periods**
- **without significant side effects**

*Barden, F. W. et al.: Journal of the Maine Med. Assoc. 46:99, 1955.
Cass, L. J. et al.: Journal-Lancet 76:42, 1956.
Smith, R. T.: Journal-Lancet 70:192, 1950.

Robins

A. H. ROBINS CO., INC., Richmond 20, Virginia

In each enteric-coated tablet

Pabalate		*Pabalate-Sodium Free*	
Sodium salicylate U.S.P. (5 gr.)	0.3 Gm.	Potassium salicylate (5 gr.)	0.3 Gm.
Sodium para-aminobenzoate (5 gr.)	0.3 Gm.	Potassium para-aminobenzoate (5 gr.)	0.3 Gm.
Ascorbic acid	50.0 mg.	Ascorbic acid	50.0 mg.

Dosage: 2 tablets, q.i.d.; or as required.

FOR SAFE, EFFECTIVE STEROID THERAPY, SEE OVER

MONODRAL® with MEBARAL®

for peptic ulcer • gastro-intestinal tension and irritability

An exclusive combination designed to relieve pain, reduce tension and promote healing through effective inhibitory central and vagal-parasympathetic actions influencing all known etiologic factors in peptic ulcer.

anticholinergic • sedative

with unusually high antisecretory action • dependable antispasmodic effect • no drowsiness

Isolates the Ulcer

Each tablet contains:

MONODRAL* bromide	5 mg.
MEBARAL**	32 mg.

Dosage: 1 or 2 tablets three or four times daily. *Available* on prescription only. Bottles of 100 tablets.

Winthrop LABORATORIES
New York 18, N.Y. • Windsor, Ont.

*Controls hyperacidity and hypermotility
**Sedates without drowsiness
Monodral (brand of penthienate) and Mebaral (brand of mephobarbital), trademarks reg. U.S. Pat. Off.

A Totally New... Vastly Improved Nebulizing Method

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THE ONLY "MEASURED DOSE" METHOD

- Leakproof, spillproof bottle; medication cannot change or deteriorate.
- Dose released is always the same—does not depend on patient strength or on amount in bottle.
- Inexpensive, unbreakable, inconspicuous Medihaler Oral Adapter fits conveniently in pocket or purse.

***Medihaler-EPI™**
0.5% solution of epinephrine U.S.P.

***Medihaler-ISO™**
0.25% solution of isoproterenol HCl U.S.P.

One or occasionally two inhalations provides relief for most patients. Notably safe and effective with children. Highly economical. Bottle provides 200 applications.

In prescribing be sure to write for Medihaler-Iso (or Medihaler-Epi) AND Medihaler Oral Adapter. For refills, write for medication only.

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LOS ANGELES

XYLOCAINE® HCl SOLUTION ASTRA

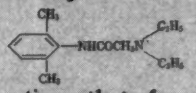
The Name That Marks a New Era in Local Anesthesia

Xylocaine provides peak values in:
• **Duration** • **Clinical Effectiveness** • **Clinical Tolerance** • **Speed**
• **Stability** • **Versatility** • **Clinical Predictability** • **Safety** • **Depth**

Trade Name: XYLOCAINE **Generic Name:** lidocaine*

Chemical Name: 2-Diethylaminoaceto-2,6-xylidide

Chemical Structure:



Potency: Two to three times that of procaine.

Duration of Action: Two to three times that of procaine.

Anesthetic Index: 1.8. **Surface Anesthetic Index:** 8.

Safety Factor: Two to three times that of procaine (because smaller concentrations and volumes are clinically as effective).

Sensitivity: Allergic manifestations and sensitizing reactions have never been reported.

Inhibition of Therapeutic Action of Sulfonamides or Antibiotics: None.

Versatility: Effective in local infiltration anesthesia; in major conduction anesthesia; in temporary therapeutic blocks for relief of pain; in topical anesthesia.

Available on Request: Descriptive literature, bibliography, and trial supply.

Supplied: Vials, 0.5%, 1% and 2% in 20 cc. and 50 cc. without and with epinephrine 1:100,000; 100 cc. vials, 1% without epinephrine. Ampoules, 2 cc., 2% without and with epinephrine 1:100,000.

Astra Pharmaceutical Products, Inc., Worcester 6, Mass.

*U. S. PATENT NO. 2,441,498

BREAK THE RE-INFECTION CYCLE OF

CONJUGAL PARTNERS

IN VAGINAL TRICHOMONIASIS

VAGINAL TRICHOMONIASIS, common in women, is now recognized as a disease whose causative agent also infects the male. The number of women harboring trichomonads "...has recently been put as high as 24%."[1]

Not uncommon in husbands—Evidence shows trichomonads can be found in from 5 to 15 per cent of the male population,[2,3] or even more. Freed reported that 28.5 per cent of men in his studies were carriers.[4] In Feo's investigation, "the incidence of non-specific urethritis cases which may be attributable to *Trichomonas vaginalis* was 36.9 per cent."[5] Karnaky found the parasites in the urethra and prostate or under the prepuce in 38 among 150 husbands with infected wives.[6]

The symptomless vector—"...many patients with trichomonas vaginitis are infected and reinfected by coitus..."[7] with husbands who may be highly infective without showing clinical symptoms.[4] Infected wives can in turn reinfect husbands.

Protection against re-infection—To break the cycle of re-infection, authorities agree that the husband should use prophylactics regularly while the wife is under treatment and until it is established that *her* infection has cleared—then until *he* is free from infection.[2,3,8,9] Karnaky advises a period of as long as four to nine months. By this time the husband's infection will usually die out of its own accord.[8] Davis states: "Obviously the man who has a chronic trichomonas infection...will continue to reinfect his wife unless he wears a sheath during coitus."[9]

Prescription of prophylactics—Seek the aid of the husband when you treat the wife. "How The Husband Can Help," a booklet for patients, explains his role in the control of trichomoniasis. Copies are available upon request. Use this booklet to gain his cooperation, make explanations easier, save your time.

In prescribing prophylactics, take advantage of Schmid product improvements to win acceptance of your treatment plan. If there is anxiety that a prophylactic might retard sensation, specify XXXX (FOUREX)® skins. Made from the cecum of the lamb, tissue-smooth and premoistened, they do not dull sensory effect. If there is a preference for a rubber prophylactic, specify the superior RAMSES® prophylactics. These are different, transparent, very thin yet strong, of natural gum rubber.

References: 1. McEntegart, M. G.: J. Clin. Path. *5*:275 (Aug.) 1952. 2. Draper, J. W.: Internat. Rec. Med. *168*:563 (Sept.) 1955. 3. Bernstine, J. B., and Rakoff, A. E.: Vaginal Infections, Infestations and Discharges, New York, The Blakiston Co., 1953. 4. Freed, L. F.: South African M. J. *22*:223 (Mar. 27) 1948. 5. Feo, L. G.: Am. J. Trop. Med. *24*:195 (May) 1944. 6. Karnaky, K. J.: Urol. & Cutan. Rev. *42*:812 (Nov.) 1938. 7. Lanceley, F.: Brit. J. Ven. Dis. *29*:213 (Dec.) 1953. 8. Karnaky, K. J.: J.A.M.A. *155*:876 (June 26) 1954. 9. Davis, C. H. (Ed.): Gynecology and Obstetrics (revision), Hagerstown, W. F. Prior, 1955, vol. 3, chap. 7, pp. 23-33.

JULIUS SCHMID, INC., *prophylactics division*
423 West 55th Street, New York 19, N. Y.

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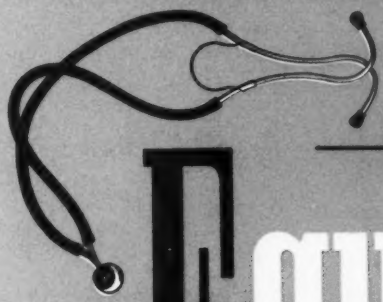
anxiety is part of EVERY ILLNESS[1]

The physically sick patient faces two stresses—the sickness and the anxiety that it brings.[1] All too often, the anxiety is a threat to the patient's progress. It may intensify symptoms, give uncertainty to therapy, and impair rapport.

To combat the anxiety component of physical illness, EQUANIL promotes equanimity, relieves muscle tension, and encourages normal sleep.[2] By these specific actions, EQUANIL gives breadth to the treatment program—expands the physician's resources.

Supplied: Tablets, 400 mg., bottles of 50.
Usual Dose: 1 tablet, t.i.d.

1. Braceland, F.J.: Texas State J. Med. 51:287 (June) 1955.
2. Lemere, F.: Northwest Med. 54:1098 (Oct.) 1955.



E

Equanil*

Wyeth
Philadelphia 1, Pa.

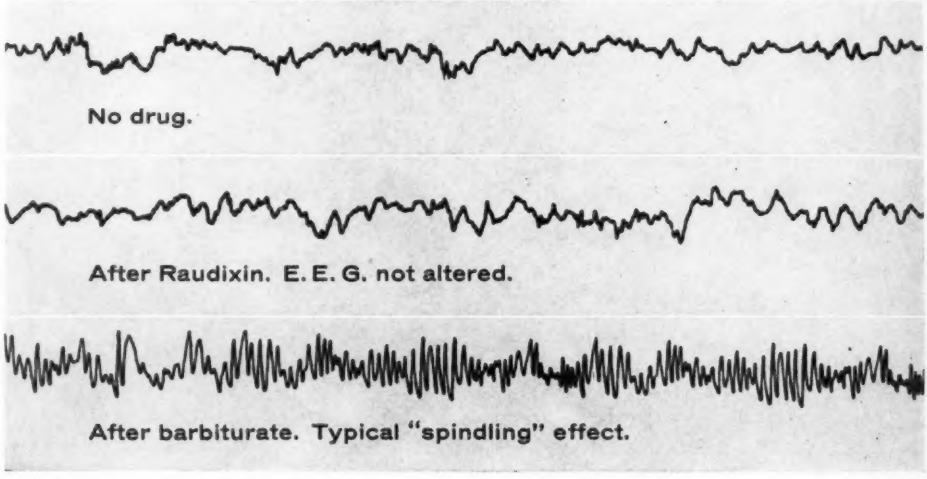
Meprobamate
(2-methyl-2-n-propyl-1,3-propanediol dicarbamate)

Licensed under U.S. Patent No. 2,724,720 *Trademark

anti-anxiety factor with muscle-relaxing action

WHAT IS THE DIFFERENCE BETWEEN A TRANQUILIZER AND A SEDATIVE?

Comparison of the effect of Raudixin (tranquilizer) and a barbiturate (sedative) on the cortical electroencephalogram



No drug.

After Raudixin. E. E. G. not altered.

After barbiturate. Typical "spindling" effect.

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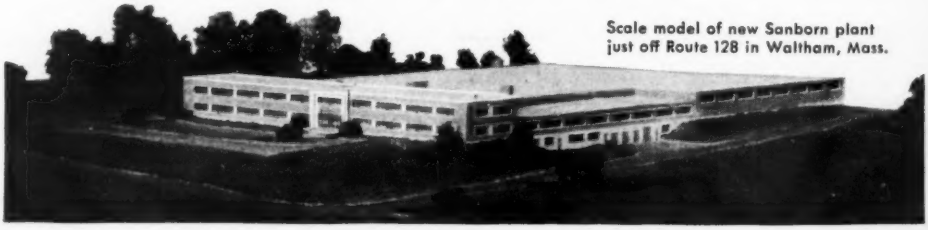

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THE REAL QUESTION

To the physician on the firing line of daily practice, the question of "how old is old?" seems academic. To him, a more valid question is "How can I allay the effects of the aging process?"

FIVE PROBLEMS IN AGING

The answer, according to most authorities, is manifold, for five treatable problems seem to predominate. One, obviously, is gonadal hormone decline. Another is mild anemia. A third is the decreased production of gastric and digestive enzymes. Mineral-vitamin deficiency is the fourth. And the fifth—perhaps most important—is inadequate high-quality protein intake.

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In spite of jokes to the contrary, the patient who states in the professional office that "old age is creeping up" is a rare bird indeed.

Seldom is old age the presenting complaint. Thus the physician, after correcting the specific complaints, must re-evaluate the whole person to judge his candidacy for "preventive geriatrics."

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l-Thyroxine	0.1 mg.
Ethinyl Estradiol	1 mcg.
Methyltestosterone	1 mg.
Liver Fraction I	25 mg.
Ethyl Alcohol	0.5 cc.

Dosage: One teaspoonful twice daily before meals, or as required.

Supplied: In 16 fluid ounce bottles, prescription only.

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1. Rehfuss, M. E.: Indigestion, Philadelphia, W. B. Saunders Co., 1943, p. 322.
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1. Johnston, T. G., and Cazort, A. G.: J. Allergy 27:90, 1956. 2. Schwartz, E.: New York J. Med. 56:570, 1956. 3. Schiller, I. W., et al.: J. Allergy 27:96, 1956.

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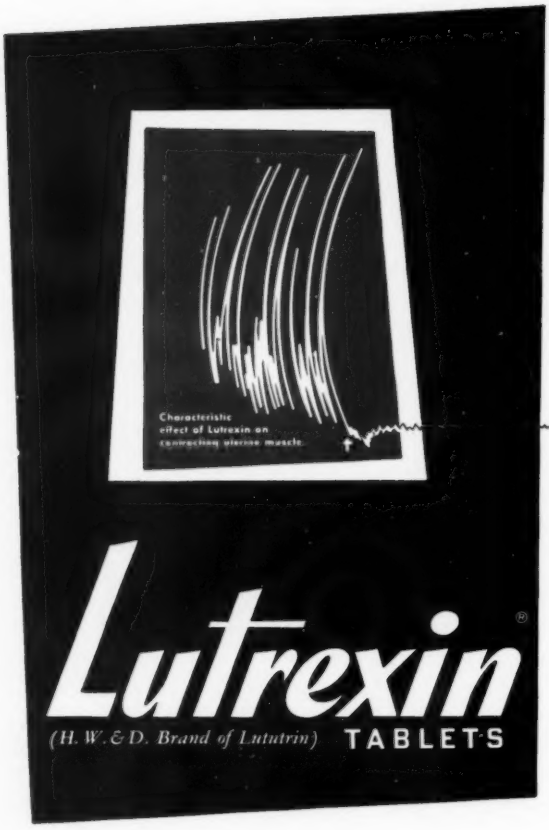

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1. *Jones, Georgeanna S. and Smith, Frank: Am. J. Obstet. Gynecol., Vol. 67: No. 3, 628-633, 1954.*
2. *Majewski, J. T. and Jennings, T.: Obstetrics & Gynecology, Vol. 5, No. 5, 1955.*

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Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

August 1956

An Epidemic of Histoplasmosis Among School Children in Arkansas*

TOM D. Y. CHIN, M.D., PETER E. NEY, M.A., BENJAMIN N. SALTZMAN, M.D., GEORGE B. PAXTON, M.D., JENNIE H. RAKICH, R.N., MILDRED WARE, R.N., MARGARET WHITMORE, R.N., and MICHAEL L. FURCOLOW, M.D.,† *Kansas City, Kan.*

This paper recounts the epidemiologic studies of an outbreak of histoplasmosis in an Arkansas school. The source of the fungus could not be determined.

THE OCCURRENCE OF HISTOPLASMOSIS IN AN EPIDEMIC FORM was first encountered in Plattsburg, New York, by Nauen and Korns[1] in 1938, at which time it was described as an outbreak of "acute miliary pneumonitis." During the following few years other outbreaks were observed elsewhere. Since the nature of the disease was not understood, they were variously referred to in the literature as instances of "unusual pulmonary disease,"[2,3] "cave sickness,"[4] "pneumonitis of unknown etiology,"[5] "miliary granulomatous pneumonitis,"[6] and "primary atypical pneumonia."[7] The first report establishing *Histoplasma capsulatum* as a probable cause of epidemic pulmonary disease was published in 1952 by Loosli and associates.[8] In 1953, Furcolow and Grayston[9,10] reviewed 13 of the epidemics and made a study of their etiologic and epidemiologic features. Up to the present more than 30 epidemics involving over 370 individuals have been recognized.[11] The most recent major outbreak was encountered among a group of children in an elementary school in Mountain Home, Arkansas, during the spring of 1955. The epidemic was investigated by a team of epidemiologists from the Communicable Disease Center, Public Health Service, in collaboration with state and local health personnel. It is the purpose of this paper to present the collected data and to describe the principal epidemiologic features observed.

*Read before the Section on Public Health, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Department of Health, Education, and Welfare, U. S. Public Health Service, and Baxter County Health Department, Mountain Home, Ark.; and the Kansas City Field Station, Epidemiology Branch, Communicable Disease Center, University of Kansas Medical Center, Kansas City, Kan.

Methods of Study

The investigation was begun on March 4, 1955. Clinical and epidemiologic records were obtained from 36 reported cases. During the time of the study 13 of these patients were still ill and confined at home. The remainder had already recovered and returned to school. A complete history and physical examination were performed on each of the 13 sick children, while a detailed history was taken from those who had already recovered. Skin testing and collection of blood were done on the 13 sick children during the time of the examination. Unfortunately permission could not be obtained to perform gastric washings and bone marrow punctures. Throat washings, however, were collected from 7 of the patients for mycologic studies.

An effort was also made to study as many children as possible in the elementary school in order to ascertain the incidence of inapparent infection by means of skin test, serologic tests, and chest x-ray. There were 386 children between the ages of 6 to 10 enrolled in the first five grades. A total of 361 children were included in the study. A group of sixth graders from another school, located approximately one-half mile away, was selected as con-

trols. It should be mentioned that the children in the control group were older than any of the children involved in the school epidemic, and the majority of them were graduated from the elementary school the previous year. During the latter part of the investigation studies were also conducted in other schools in the county, and the results of this county-wide survey will be reported in a later publication.

Histoplasmin and tuberculin skin tests were done on all children.* One-tenth (0.1) ml. of the properly standardized antigen was injected intradermally and the reaction was read at the end of 48 hours. An area of induration five or more millimeters in diameter was considered positive.

Blood samples were collected at the time of skin testing (approximately 17 days after the peak of the epidemic) and second samples were taken about three weeks later. Some third samples were collected five months after the first bleeding. All sera were tested for antibodies against *Histoplasma capsulatum* by both the complement fixation test using whole yeast phase antigen,[12] and the precipitin test using soluble yeast phase antigen.[13] A titer of 1:8 or higher was considered positive.

All sera were tested for complement fixing antibodies against psittacosis. Twenty-nine samples of convalescent sera were also tested for complement fixing antibodies against Q fever, 5 for influenza and APC group of viruses, and 18 for presence of cold agglutinins.†

Chest x-ray films were taken on all of the 36 reported cases. In addition all positive reactors to either of the skin tests, as found in the survey, had an examination with the 70 mm. chest x-ray. A 14 by 17 inch chest film was taken on those individuals showing definite or suspicious lesions on the 70 mm. film.

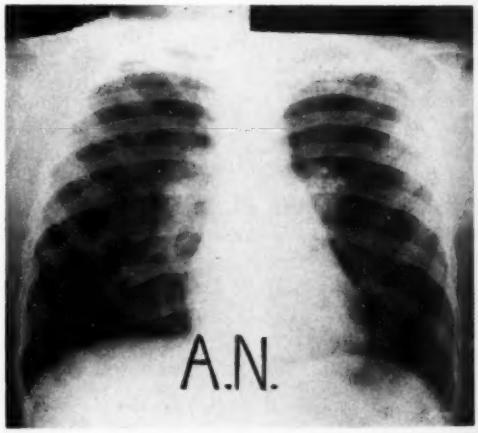
Soil samples obtained on two different occasions were examined for pathogenic fungi. The methods used consisted of inoculating soil suspensions in saline intraperitoneally into laboratory white mice and culturing their livers and spleens three to four weeks later.[14]

Six parakeets were kept in the classrooms of the school as pets by the pupils. Five of these parakeets were sacrificed and virus studies were performed by both mouse and embryonated egg inoculations. Some of the mice were also cultured for pathogenic fungi at the end of one month's observation.

Clinical Characteristics

The clinical study was based on the 36 reported cases. In general the clinical picture was similar to that described in previous outbreaks.[2,4,5,7,9] The disease was an acute febrile illness, characterized by a sudden onset of fever, general malaise, weakness, and lassitude. The temperature ranged from 101 to 106° F. with most of the patients having a fever of 102 to 104° F. Some of the patients also complained of headache and anorexia. The chest complaints were remarkably mild, with nonproductive cough and vague chest pain. Only one-third of the patients gave a history of cough, and less than this proportion had chest pain. One patient gave a history of some dyspnea. The course was self-limited and the duration of illness lasted from a few days to four or five weeks, with the fever falling by lysis. The physical findings were strikingly few. Antibiotics such as penicillin, streptomycin, Aureomycin, and Terramycin had no significant effect on the course of the illness.

FIG. 1

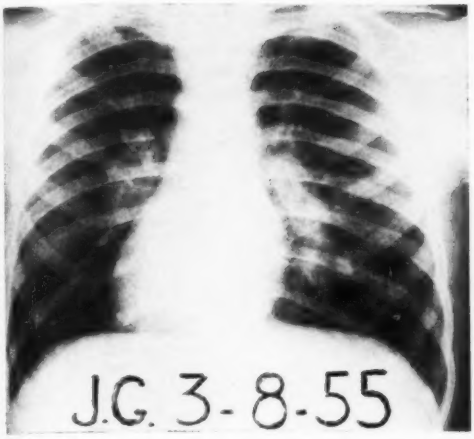


Moderate hilar lymph node enlargement with few scattered infiltrations.

*Coccidioidin and blastomycin were used on 11 of the more severely ill patients with negative reaction.

†The serologic tests for histoplasmosis were performed by Dr. S. B. Salvin and those for psittacosis, Q fever, influenza and APC viruses by Dr. David Lackman, Rocky Mountain Laboratory, Hamilton, Montana.

FIG. 2

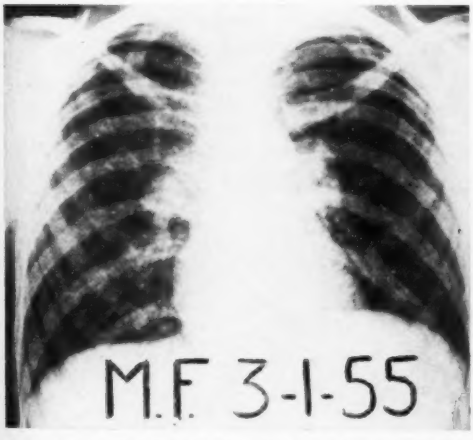


Markedly enlarged hilar lymph nodes with scattered infiltrations.

On chest x-ray examination varying degrees of infiltration ranging from a few scattered to diffusely disseminated discrete infiltrations throughout both lung fields were observed (Figs. 1 to 4). Enlargement of the hilar lymph nodes was usually present.

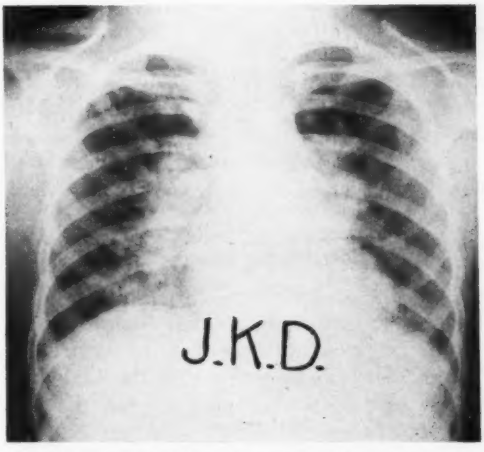
The diagnosis of histoplasmosis in this epidemic was based on a history of illness, skin reaction, serologic response and chest x-ray. Of the 36 patients examined, all had a positive histoplasmin skin test except for one patient who was not skin tested; none reacted to tuberculin. Twenty-five of the 36 had positive serologic tests for histoplasmosis, 27 had x-ray evidence of infection, and 32 had either positive serologic tests or positive x-ray examination. Twenty-two individuals had both positive serologic tests and x-ray findings. Of the 36 reported cases 19 paired sera were available for study and in some of the cases third samples were also tested. Eleven of the paired sera showed a change (either a rise or fall) of fourfold or greater in either the precipitin or complement fixing antibody titer. It is of interest to note that among the 11 positive samples a fall in precipitin titers was more frequently observed, while falling complement fixing antibody titers occurred equally frequent as rising titers. High precipitin titers were observed in most of the positive sera with three having titers as high as 1:1280. One patient had no detectable antibodies in the first blood specimen, but both types of antibodies were present in significant titers in the second sample. In two of the patients significant fall of complement fixing antibody titers was observed only on the third sera, which were taken about five and a half months after the peak of the epidemic. The frequency of positive serologic tests in the entire group, the higher percentage of positive precipitin test as compared with that of the complement fixation test on the first sera, and the changing titers between the different bleedings all support the etiologic relationship.

FIG. 3



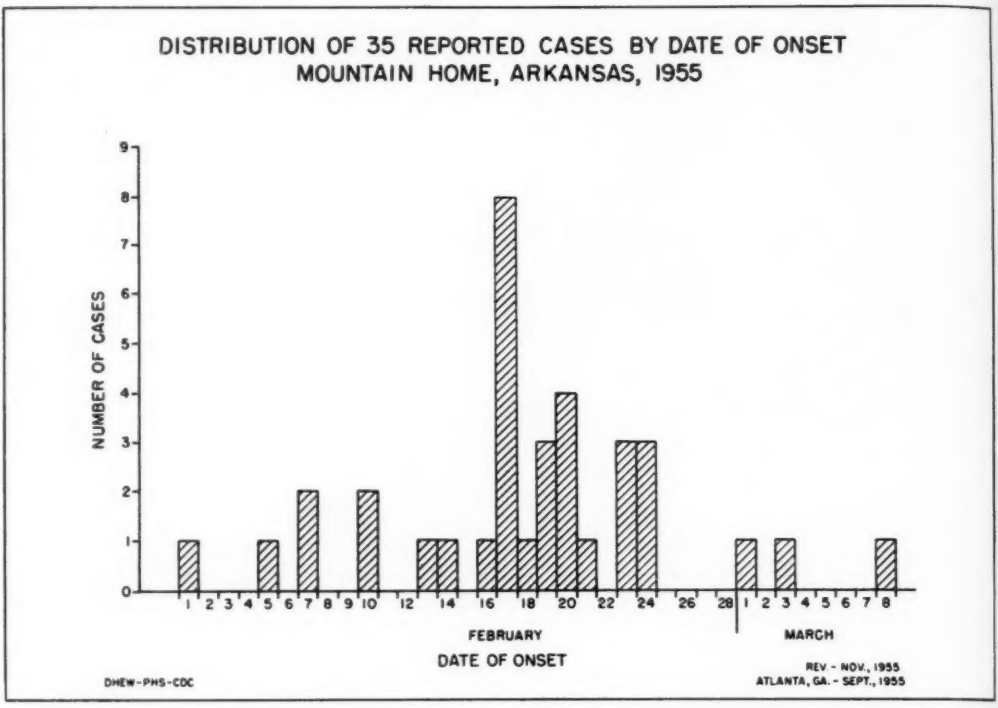
Diffusely disseminated infiltrations throughout both lung fields with moderate hilar lymphadenopathy.

FIG. 4



Lymphadenopathy with perihilar infiltration and extensive parenchymal involvement.

FIG. 5



Serum from only one of the 36 reported cases had significant psittacosis antibody titer, i.e., no detectable antibodies in the first serum, 1:16 in the second serum. This serum, however, also contained significant precipitin and complement fixing antibody titers for histoplasmosis. All the sera tested were negative for Q fever, influenza, APC viruses and cold agglutinins. Hemogram and urinalysis were done on only a few of the patients, and the results were within normal limits. Throat washings obtained from 7 of the patients were negative for pathogenic fungi. The virus and fungus studies of the parakeet tissues were also negative.

Epidemiologic Observations

Epidemic Curve. The distribution of 35 reported cases by date of onset (date of onset of one case was not known) is illustrated by figure 5. It will be noted that the first case was recognized on February 1, with the last one recorded on March 8. The peak of the epidemic occurred on February 17 (8 cases), and almost two-thirds of the patients had dates of onset between February 17 and 24.

Attack Rates. The number and percentage of reported cases occurring in each classroom are tabulated in table 1. The attack rate for the entire school was 9 per cent. It is of interest to note that 14 cases or an attack rate

TABLE 1

NUMBER AND PERCENTAGE OF REPORTED CASES AMONG CHILDREN ATTENDING MOUNTAIN HOME ELEMENTARY SCHOOL, BY GRADE, ARKANSAS—SPRING—1955

Grade	*Number Enrolled*	*Number Ill*	*Per Cent Ill*
1 A	30	3	10
1 B	30	1	3
1 C	31	1	3
2 A	28	14	50
2 B	30	2	7
2 C	31	2	6
3 A	43	3	7
3 B	42	3	7
4 A	28	2	7
4 B	30	3	10
5 A	32	0	0
5 B	31	2	6
Total	386	36	9

TABLE 2

NUMBER AND PERCENTAGE OF POSITIVE HISTOPLASMIN REACTORS BY GRADE, MOUNTAIN HOME, ARKANSAS—SPRING—1955

Grade	Number Tested	Number Positive	Per Cent Positive
1 A	30	26	87
1 B	25	22	88
1 C	28	23	82
2 A	27	26	96
2 B	25	23	92
2 C	31	24	77
3 A	42	36	86
3 B	35	34	97
4 A	24	21	88
4 B	30	27	90
5 A	30	27	90
5 B	29	26	90
Total	356	315	88
Sixth Grade (Control)	48	33	69

of 50 per cent was observed among the children in grade 2-A. There was no significant sex difference.

Histoplasmin Skin Test Survey. A total of 356 children in the elementary school were given intradermal tests with histoplasmin and tuberculin. These tests were also performed on 48 sixth graders (control group) from another school. It will be seen from table 2 that 88 per cent of the children were positive histoplasmin reactors (only 12 individuals reacted to tuberculin), as compared with 69 per cent of the control group, even though children in the latter group were older. The percentages of positive histoplasmin reactors for all the grades in the school were uniformly high, ranging from 77 in grade 2-C to 97 in grade 3-B. The percentage of positivity for the children in grade 2-A was 96. When the histoplasmin sensitivity in this school was compared with that of the other schools in the same county (11) it was evident that the prevalence in the Mountain Home elementary school was consistently higher than that of the others. This difference, however, disappeared in the high school.

Serologic Survey. The results of serologic tests for histoplasmosis are summarized in table 3. One hundred children, or 34 per cent of the school population, were positive, while only 5 per cent of the control group gave a positive test. The highest percentage of positive tests was observed among the children in grade 2-A (68 per cent). It should be pointed out that among these blood samples, a high percentage gave a positive precipitin test. This was particularly noticeable among the samples drawn during the first bleeding. About 78 per cent (67/86) of the first blood samples were positive to the precipitin test, and in approximately 25 per cent only precipitin antibodies were detectable; over 50 per cent were positive to both the precipitin and the complement fixation test. This finding of precipitin antibodies in a large proportion of the samples suggests that the epidemic was of recent occurrence.[15]

X-ray Survey. A total of 293 children had chest x-ray films taken. As shown in table 4,

TABLE 3

NUMBER AND PERCENTAGE OF CHILDREN WITH POSITIVE SEROLOGIC TEST FOR HISTOPLASMOSIS BY GRADE, MOUNTAIN HOME, ARKANSAS—SPRING—1955

Grade	Number Tested	Number Positive	Per Cent Positive
1 A	27	8	30
1 B	22	7	32
1 C	24	3	12
2 A	25	17	68
2 B	21	9	43
2 C	28	9	32
3 A	32	8	25
3 B	27	10	37
4 A	18	5	28
4 B	21	5	24
5 A	24	10	42
5 B	25	9	36
Total	294	100	34
Sixth Grade (Control)	42	2	5

TABLE 4

NUMBER AND PERCENTAGE OF X-RAYS SHOWING DEFINITE LESIONS ON POSITIVE HISTOPLASMIN REACTORS BY GRADE, MOUNTAIN HOME, ARKANSAS—SPRING—1955

Grade	Number Tested	Number Showing Definite Lesions	Per Cent Showing Definite Lesions
1 A	26	9	35
1 B	20	2	10
1 C	21	1	5
2 A	26	10	38
2 B	21	7	33
2 C	23	2	9
3 A	34	4	12
3 B	31	9	29
4 A	20	5	25
4 B	26	6	23
5 A	24	6	25
5 B	21	5	24
Total	293	66	23
Sixth Grade (Control)	32	1	3

66, or 23 per cent, of the films were interpreted as having definite lesions as compared with only 3 per cent for the control group. Again the highest percentage of positive readings (38 per cent) occurred among the children in grade 2-A.

Discussion

Based on the evidence presented it may be concluded that the Mountain Home outbreak was one of epidemic histoplasmosis. Although *H. capsulatum* was not recovered from any of the patients, the etiology was well supported by the clinical characteristics of the illness, skin reaction, serologic response and chest x-rays.

The Mountain Home epidemic is the first major outbreak of histoplasmosis observed among children. It is the largest epidemic recorded. Although only 36 cases were reported, the serologic and x-ray survey conducted in the elementary school indicates that approximately 146 cases occurred among the 361 children surveyed. This total of 146 cases includes all persons with positive serologic tests, positive x-ray findings, or both. These cases ran the entire gamut of infection, ranging from inapparent to severe. The spectrum of disease shows the variability of the manifestations of this fungus infection.

Since the rate of histoplasmin reactors among natives of the county is rather high (approximately 50 per cent among grade school children, exclusive of Mountain Home) it is obvious that many of these children had probably been infected prior to the exposure which created the epidemic. It seems probable that all the children in the school were exposed and that those who had been previously infected and were presumably immune reacted with an immediate illness. Examination of the data further suggests that those who were previously uninfected responded to the infection 7 to 14 days after exposure with a more severe clinical illness and caused the so-called epidemic. This possibility is supported by a rise in absenteeism in the school about February 1, which apparently was never associated with severe enough symptoms to cause concern. This matter will be considered in full in a later paper.

Attempts to establish a common source of infection outside of the school have failed. In the reported epidemics of histoplasmosis[10] common activities such as shoveling pigeon excreta in a school house, cleaning out chicken coops and farm buildings, or working in a cave or storm cellar were found to be associated with infection. In the present study no single incident of unusual group activity outside the school, such as picnicking, visiting a farm or a cave, could be elicited.

There is little doubt that the children acquired their infection within the environs of the elementary school. The occurrence of an excessively high prevalence of histoplasmin sensitivity and positive serologic reactions among these children, as compared with a control group, certainly points to this conclusion. Inquiries revealed that in May, 1953, a number of loads of chicken manure had been dumped on the school grounds. These piles of manure were slowly scattered and the last was disked into the ground in September, 1954. At the time of study, however, there was no gross evidence of manure on the grounds and it is unlikely, due to the passage of time, that this manure furnished a source for the infection. It is also conceivable that the infection had been going on for some time, and the epidemic was brought to a focus by the recognition of the more seriously ill cases that had their onset during February. This appears unlikely because of the rather definite epidemic curve observed.

The fact that grade 2-A had more cases, had the highest prevalence of positive serologic reactions and of x-ray findings certainly suggests that the infectious source centered about this room. The only finding that might satisfy this assumption was connected with a load of coal which was obtained from an open pit mine, located about 275 miles from Mountain Home. This coal was delivered and dumped just outside the windows of classroom 2-A on January 29. On February 1 and 2 it was shoveled into the basement through the chute windows which were located just below the windows of the classroom. Further inquiries indicated that an extremely dusty situation was created by the shoveling, and the dustiness was accentuated by the daily operation of the school buses which were passing over the coal dust scattered outside the classroom. If the coal were contaminated with the spores, the cause of the high incidence

rate would have been obvious. This was made more likely by the fact that the school buses were loaded with children on this side of the building and the prevailing winds were toward the school house. Also, the teacher who had a severe illness diagnosed as histoplasmosis during the epidemic was in the habit of standing in an open window in 2-A to direct the loading of her children on the school bus. Laboratory examination of the coal dust and soil samples collected on two occasions at the school and at the open pit mine, however, failed to reveal pathogenic fungi.

Another less likely possibility was centered on a chicken house about one-tenth of a mile from the school but located on the south side so that the prevailing winds blew toward the school. No major cleaning of this chicken house took place except once, on February 12, when the epidemic was already on the ascending phase. This source appears unlikely because of the rather sharp focalization of the attack in grade 2-A. Also, cultures of material from the chicken house have failed to show the fungus.

In summary, it appears from epidemiologic, serologic and clinical findings that the coal represents the most likely source of infection. However, *H. capsulatum* was not recovered from the coal or dust samples.

Summary

1. Clinical and epidemiologic features of an outbreak of histoplasmosis occurring among a group of children in an elementary school in Mountain Home, Arkansas, during the spring of 1955 have been described.

2. There was a total of 36 reported cases; however, based on the results of the serologic and x-ray survey in the school, approximately 146 children were probably infected.

3. Significantly higher percentages of histoplasmin sensitivity, positive serologic reactions for histoplasmosis, and positive chest x-ray findings were found among the children in the school, as compared with a control group.

4. Epidemiologic evidence indicates that the children probably acquired their infection at the school.

5. Possible sources of infection have been discussed.

Acknowledgments

Grateful acknowledgment is made to Dr. J. T. Herron and to Dr. A. M. Washburn of the Arkansas State Department of Health for their cooperation in conducting this study. The assistance of Dr. James C. Dunbar, practicing physician and Mr. Harold L. Overbey, Superintendent of Schools, Mountain Home, Arkansas, is especially appreciated. Thanks are also due to Mr. V. E. Medlock of the Arkansas State Department of Health for taking most of the chest x-rays. Financial assistance of the Arkansas State Tuberculosis Association is gratefully acknowledged.

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Discussion (Abstract)

Dr. Benjamin N. Saltzman, Mountain Home, Ark. In discussing this excellent paper I feel that it is important that some comment be made on the events leading up to this study. I am a practicing physician and part-time county health officer in the town of Mountain Home, Arkansas, population approximately 2,500.

For three weeks a series of puzzling illnesses occuring in grade school children had plagued me. Each case showed low grade fever, moderate malaise, and nothing else.

An x-ray film taken on one of my little patients gave me the first clue to the disease. The film looked like either miliary tuberculosis or histoplasmosis. This child was not sick enough to have miliary tuberculosis so a tentative diagnosis of histoplasmosis was made. My previous acquaintaince with histoplasmosis

was limited to the observation of a picture of an x-ray film in a text book I had read as a junior medical student in 1939. Reading again on the subject gave me little more information than I already possessed. Present-day literature is still rather vague concerning this disease.

The "wonder drugs" did nothing for my patients and believe me, I tried every one! The parents and the school authorities were clamoring for action. They were not pleased with my diagnosis, especially since I could not show results.

A phone call to the Arkansas State Health Department resulted almost immediately in the information that a United States Public Health Service team would be in my community in just 24 hours to help with the situation. Dr. Tom Chin and Dr. George Paxton, of the United States Public Health Service, University of Kansas Medical Center, made their welcome appearance and I was able to heave a sigh of relief. They took over immediately with my blessing and almost at once the town settled down. It was a case of the marines having landed, and the situation being well in hand.

The entire study was one of the utmost in cooperation. The State Health Department and the district and county health nurses went all out to provide the necessary authority and aid for the work that was to be done. The townspeople cooperated willingly. They were anxious to discover the cause of the malady affecting their children and there were no refusals for any tests requested.

Mountain Home became a good sized laboratory. The physicians in the community cooperated in providing large chest x-rays at less than cost. The State Tuberculosis Association provided a mobile unit for small films and also paid the necessary expenses for the large films. Civic leaders and townspeople provided the necessary clerical help. The school board paved the way for complete ease of operation. This was truly an adventure in cooperation and service.

The findings of the public health service team were significant and will lead to further study. The recommendations made were specific and of benefit to our community.

Incidentally, if you need your streets paved in your own town, have a public health service team find histoplasmosis. There are very few dusty, unpaved streets remaining in Mountain Home.

The entire study proved to me that people are interested in health and are willing to cooperate with the medical profession. We need but ask. The paper itself stresses the importance of the work being carried on by the United States Public Health Service. It should make us, as physicians, aware of the fact that histoplasmosis does exist and that the histoplasmosis belt is becoming ever wider in the United States.

No private physician or group of physicians could possibly have done the work involved, and in such a well-organized manner. The study suggests that epidemics do still occur and that histoplasmosis may well be the cause of the infection. Family doctors would do well to familiarize themselves with the symptomatology or lack of symptomatology in histoplasmosis and consider it in every case of undetermined fever.

Further Comments on Medical Journals in 1848

In the course of half a century from the establishment of the first of the Medical Journals, their number has been gradually rising, until at the present time, at least twenty are known to be in existence. Some principle in addition to the wants of the reading community, must exist to account for such inordinate fecundity in this particular department. This is to be found in the homely fact, that a medical journal is a convenient ally and advertising medium for public institutions and publishing establishments, and that by the help yourself system so generally established, it is not necessarily much harder to edit a medical journal than to furnish the "notes and additions" to the work of a British author. Still, the general character of these journals is respectable, and of several among them highly creditable to the state of medical science. Every year shows that exact observation is more and more valued, and that a better literary standard is becoming gradually established.

—From the report of the committee on medical literature. *Transactions of the American Medical Association,* Vol. 1, 1948, p. 283.

Experimental Studies and Clinical Evaluation of Linear Growth Stimulation*

WAYNE S. MONTGOMERY, M.D., *Asheville, N. C.,* and
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Attempts to stimulate growth in the bones of legs affected by poliomyelitis, for example, have been generally unsuccessful. Further experimentation and study will be needed before an answer to this problem may be forthcoming.

INEQUALITY OF THE LEG LENGTH IN THE ADULT predisposes to many pathologic changes due to the abnormal stresses created by lateral displacement of the center of gravity. Were we able to prevent or minimize this during childhood, the ultimate in preventive orthopedics would be achieved.

It is common knowledge that overgrowth of the femur or tibia is seen in: (1) fractures, (2) hemihypertrophy, (3) neurofibromatosis, (4) osteomyelitis, (5) burns, and (6) with vascular lesions of an extremity. These overgrowths can be consolidated under four physiologic processes. The first process concerns the local acceleration of osteogenesis during absorption of a foreign body such as ivory. Secondly, an inflammatory response occurs during establishment of colloidal solutions when two different metals are implanted in bone. Thirdly, alterations of oxygen tension in an extremity vary growth as seen in congenital arteriovenous fistulas. Finally, during repair and remodeling of bone, linear growth likewise is accelerated.

The material contained in this presentation is twofold in nature. First, an attempt was made to experimentally stimulate longitudinal growth of the femur and the tibia in rabbits by ivory implantation, periosteal stripping, with and without postoperative immobilization. Secondly, a group of 32 patients underwent a surgical procedure aimed at stimulation of longitudinal growth. Various members of the staff of the Campbell Clinic performed these operations. The results of these two investigative studies are reported herewith.

*Read before the Section on Orthopedic and Traumatic Surgery, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Campbell Clinic, Memphis, Tenn.

Experimental Study

The most desirable features of all methods of experimental attempts at growth stimulation were weighed. Use of an absorbable material such as ivory seemed to offer the greatest hope as no other implant had proved superior. Stripping of the periosteum on the metaphyseal side of the epiphyseal line would prolong the reparative process. As so many patients are placed in casts following the stimulating attempts in conjunction with fasciotomies, osteotomies or tendon transfers, the effect of passive hyperemia of disuse versus the active hyperemia associated with the stimulus of weight-bearing was considered. Thus half of the experimental animals were immobilized postoperatively for two weeks, with casts on the treated extremity. Operation was performed on two month old rabbits which compare with a six to nine year old child in growth scales.

In the rabbits treated without casts three weeks postoperatively there is seen microscopically the orderly maturation of cartilage cells. Three weeks postoperatively a rabbit treated in a cast reveals mature disintegrating vacuolated cells with poorly formed osteoid. One might assume that the microscopic picture of the rabbit treated with a cast represented a damaged epiphyseal line. On the contrary however, the "sick" bone actually had overgrown 2 mm. in the tibia, and the femora were of equal length. It is felt the immobilization contributed to a passive hyper-

TABLE 1

GROUPING OF RABBITS

Died during operation	2
Group I (immobilized postop.)	22
Group II (not immobilized postop.)	23
Total	47

emia which created a temporary stimulus of the bone to accelerate its rate of growth. As will be presented later, the stimulus of weight-bearing being absent early resulted in a retarding effect of the overall length of the extremity at six months.

Table 1 shows the division of the 47 rabbits into Group I and Group II. Table 2 shows that Group I gave 15 rabbits for study at six months, and table 3 offers in Group II, 16 animals treated without a cast. A high number of technical failures stemmed from the enthusiasm for the surgeon to place the ivory adjacent to the epiphyseal line in the metaphysis. Thus table 4 shows the final analysis of all the bones. Group I revealed that 4 bones overgrew 1 mm. or more, 10 bones shortened 1 mm. or more, in 6 the bones were equal, and 10 bones were technical failures. The animals in Group II treated without cast revealed 11 bones stimulated 1 mm. or more, 8 bones shortened, 4 bones unchanged, and 9 bones technical failures.

Conclusions drawn from these experimental studies were that stimulation of growth was possible but not consistent enough nor of great enough magnitude when present to be of significance. Microscopically and numerically it appeared that postoperatively weight-bearing favored utilization of exogenous implants and stimulation appeared more likely. Periosteal stripping theoretically should prolong the reparative inflammation.

Clinical Evaluation

A total of 32 children were followed a minimum of 12 months and a maximum of 54 months with an average follow-up of 28 months. Phosphoralized cod liver oil was attempted as a bone marker early in the study; however the great variable known as "the human element" made this an insurmountable problem. Various bone markers were considered such as the finely tooled marker advocated by Blount.[1] Due to the thickness of the cambium layer of the periosteum in children and the known migration of the periosteum on the cortex of the metaphysis and diaphysis as pointed out by Lacroix,[2] there was too easy an avenue of error in evaluation of growth increments. Reliance was placed on growth lines when present, clinical measurements, and calibrated x-ray studies.

Brass screws were used early as implants with frequent inflammation of the wounds being noted postoperatively. In no cases was there evidence of pus. In 1952 and 1953 ivory pegs were implanted.

The 32 cases were divided into two groups. Fifteen of the children had a dysplasia or aplasia with essentially normal motor power of the extremities. Seventeen had residual effects of poliomyelitis with one or both extremities involved with motor weakness.

As might be expected in the 15 patients having dysplasia, all had an abnormal gait from such conditions as a bowed tibia, congenital absence of the fibula, and coxa vara. Table 5 illustrates that in this group two patients received one-half to five-eights of an inch increase in the length of the bone, one patient had less than half an inch, but more than a quarter of an inch, six had inconclusive results, and six received no benefit. One of the two patients obtaining a favorable result had five operative procedures, namely, two subtrochanteric osteotomies for coxa vara and three stimulating procedures, one consisting of brass screws and two of ivory pegs. Figure 1 shows the brass screws stimulated the distal femur in 9 months to overgrow 13 mm. as compared by growth lines in the metaphy-

TABLE 2

GROUP I	
(Immobilized 2 weeks postop.)	
Died of intercurrent infection	5
Sacrificed at 3 and 5 weeks	2
Available for study	15
Total	22

TABLE 3

GROUP II	
(Not immobilized)	
Died of intercurrent infection	5
Sacrificed at 3 and 5 weeks	2
Available for study	16
Total	23

TABLE 4

RESULTS OF EXPERIMENTS

	Over-growth	*Short-ening*	*Bones equal*	*Technical failure*
Group I (Cast)	4	10	6	10
Group II (No cast)	11	8	4	9

TABLE 5

GROWTH IN 32 CHILDREN

Etiology	*⅛"-½"*	*½"-¼"*	*Inconclusive*	*Failures*
Dysplasias 15	2	1	6	6
Polio 17	2	4	4	7

sis. Sixteen months after the second stimulating operation, using ivory pegs, the distal end of the femur had gained a combined total of 18 mm., the proximal end of the tibia 2 mm., and the distal end of the tibia gained 2 mm. The other patient having a favorable result gained five-eighths of an inch on a basis of clinical measurements 24 months after stimulation of the femur and tibia by ivory. One patient had a congenital dislocation of the hip, which required open reduction to achieve stability. A stimulation procedure after the hip was stable resulted in maintenance of one quarter of an inch gain after 25 months. The six inconclusive results were in patients who had stimulation in one extremity and arrested growth of the other extremity. The six failures had no common denominator.

In studying the 17 paralytic cases, the degree of paralytic involvement was classified in accordance with Stinchfield, Reidy and Barr's[3] "twenty-three muscle" test. Using this test to estimate discrepancies as compared with results offered no correlation. In the poliomyelitis cases, two gained one-half to five-eighths of an inch. One of these had a flail extremity with an estimated discrepancy of two and three-eighths inches at maturity. He now is grown with a two and an eighth inch shortening shown in films for leg length. The other patient gained five-eighths of an inch and maintained this for 17 months. The four patients with minimal stimulation were insignificantly benefited. Of the four inconclusive cases, two also were stapled and two had inconclusive measurements. Seven received no benefit whatsoever.

Considerable variability was noted in the reaction of host bone to the implants. As can be noted in figure 2 rather marked corrosion

FIG. 1

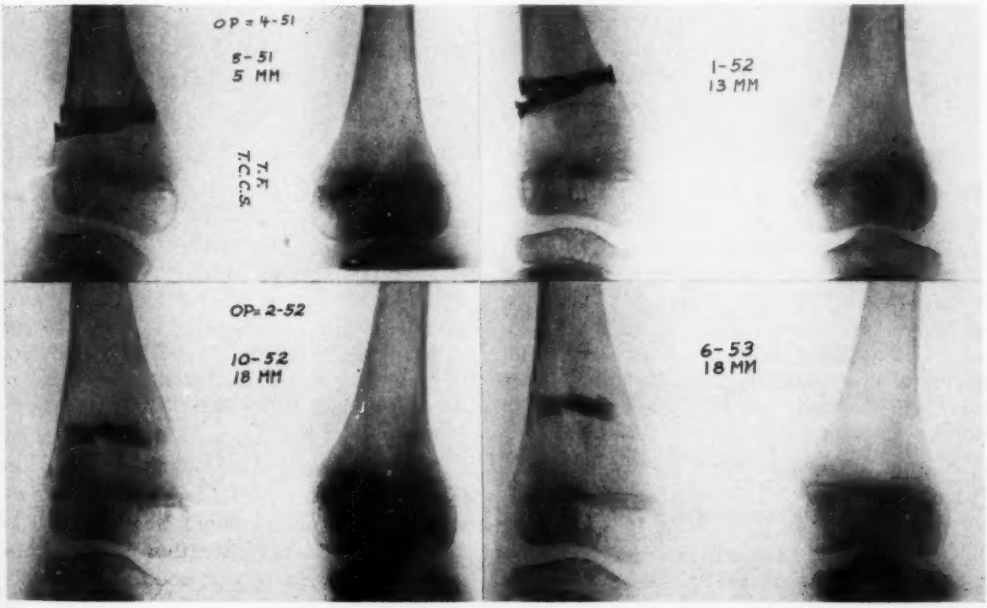
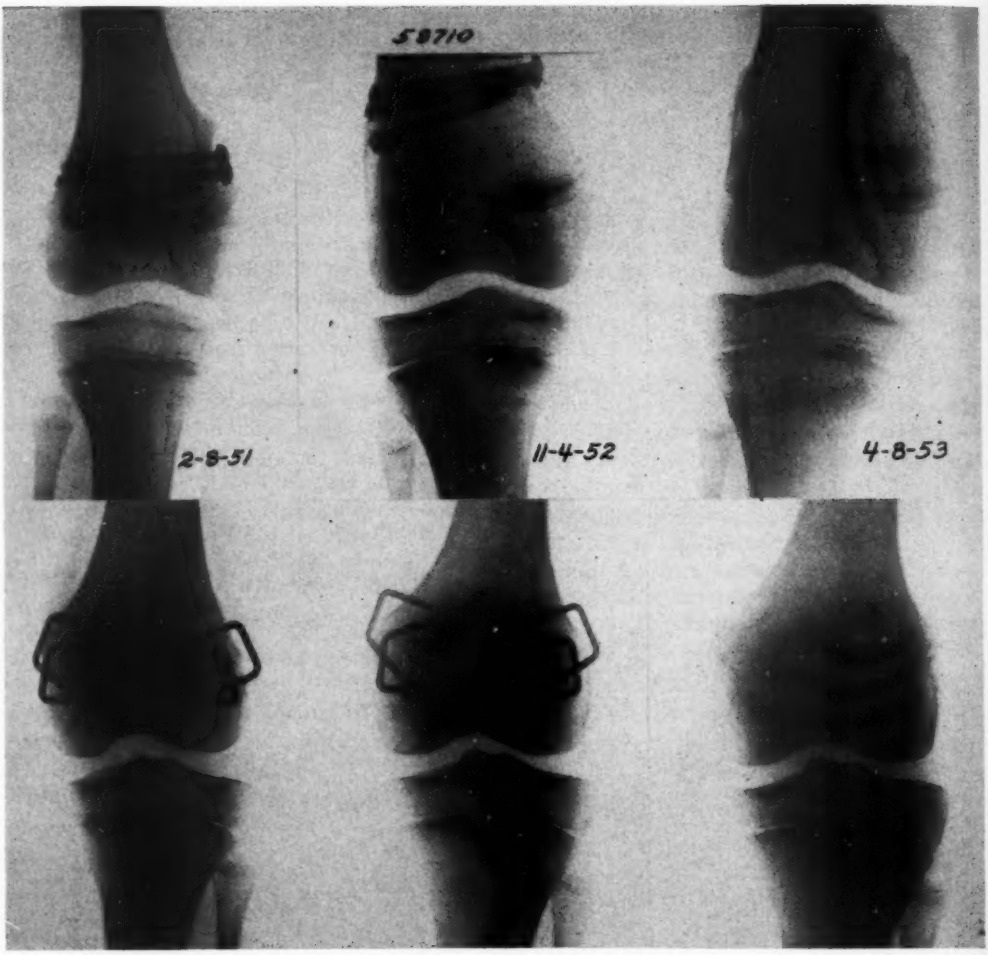


FIG. 2



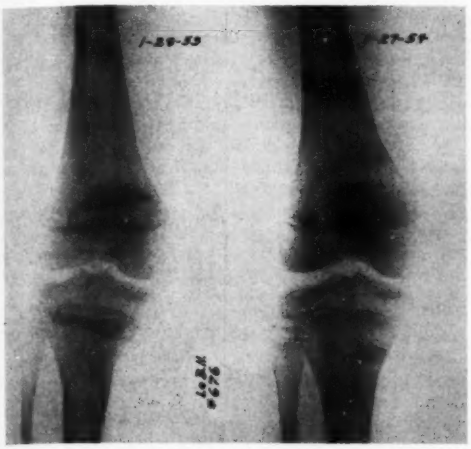
of the brass occurred. While in others the brass appeared to be walled off with a thin line of sclerotic bone surrounding the screw. Figure 3 reveals that in one year the ivory has almost lost its identity, while figure 4 shows another case one year after implant with no acceptance by the host of the implant. Impairment of tubulation in the metaphysis and diaphysis as shown in figure 4 was seen in 20 of the 32 patients. None of these variables altered the result of the stimulation procedures.

Discussion

One must thus conclude from the experimental and clinical material that the attempted stimulation of growth by use of ivory or brass implants as an elective procedure is not justified. The small gain, if present at all, can more simply be attained by a shoe lift. The stimulating procedures done in conjunction with hip fasciotomies, osteotomies, tendon transfers, or the Green-Grice paralytic flatfoot operation, may retard progression of the discrepancy in leg length.

Theoretical improvements might be as follows: Use of three ivory pegs cut to a smaller diameter would afford a larger surface of absorption and create more venous stasis as favored by Trueta.[4] Elevation of the periosteum in the metaphysis would prolong the

FIG. 3



reparative period. Early weight-bearing is desirous to convert the operative area into an active hyperemia of increased bone production as stated by Baker.[5]

Summary

1. A series of animal experiments for attempted stimulation of linear growth of one extremity revealed a low percentage of stimulation.

2. Early weight-bearing appeared to be essential for conversion of a passive hyperemia into an active hyperemia of bone production.

3. A preliminary report of 32 clinical cases revealed no justification for brass or ivory implants for attempted stimulation of growth, when performed as a single procedure.

4. Suggestions for improvement of present methods were outlined.

FIG. 4

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Discussion (Abstract)

Dr. Earnest B. Carpenter, Richmond, Va. I appreciate the privilege of discussing Dr. Montgomery's very fine paper. In the past few years, much emphasis has been placed on the need for investigation of many of the basic problems of orthopedics. Dr. Montgomery's paper very intelligently covers one of the still many unanswered problems, that of inequality of leg lengths. In the past, the problem of discrepancy in leg length has been approached by methods to shorten the good leg, or to slow down its growth. The understandable reluctance of parents to permit operation on the "good leg" combined with the realization that such operations for shortening or arresting are not always entirely satisfactory, has directed investigation toward methods of stimulating additional growth of the "bad" leg. Animal experiments on growth stimulation have been very encouraging, but unfortunately the same encouraging results cannot be duplicated in the human.

For a number of years I have been very interested in this problem of inequality of leg lengths. Stimulated by Dr. Pease's preliminary report on the use of metallic screws and ivory to stimulate growth of the distal femoral epiphysis, we began a clinical study of this problem in 1952. It was felt that to properly evaluate such a clinical study, it should include only those patients with shortening of at least one inch, and the patient should preferably be below the desired age for a shortening, or an arresting operation. To permit a proper quantitative evaluation of such a study, it was agreed that a sufficient number of such stimulation operations would be necessary, and to permit qualitative appraisal of the method no other operative procedure should be done on the "bad" leg during the period of clinical observation.

We have used a method very similar to that employed by Dr. Montgomery, with some technical variations. Our thinking on this problem was along the lines that if stimulation of the epiphysis was to be accomplished, it must be by increasing blood flow into the epiphyseal plate. This we felt could best be accomplished by blocking the intramedullary circulation with a noncorrosive foreign body, which would at the same time act as a stimulant to increase blood flow

to the epiphysis. Small pieces of ivory were used as a stimulating material. During a period of 20 months, we operated on 30 patients in the following manner. The distal femur was fenestrated in its lower third, proximal to the flare of the condyles. The periosteum in this area was stripped proximally and distally for at least two inches. The medullary contents were thoroughly curetted, and the cavity produced by this curettage was then tightly packed with small chips of ivory so as to occlude as completely as possible the medullary circulation in this area. The upper third of the tibia was treated in a similar manner. The fenestration window was replaced in each bone after packing the medullary canal with ivory. A cylinder cast was applied for three weeks, and the patient was permitted weight-bearing as soon as postoperative edema and discomfort had subsided.

Each patient was examined at three months' intervals, at which time, in addition to clinical leg length measurements, x-ray films for leg length measurement were made. Each patient has been followed for a minimal period of two years, during which period of time I believe we have been able to honestly and accurately evaluate this method of stimulation. A more detailed report on this study is to be made at a later date. Time does not allow a detailed analysis in this discussion. A total of 33 operations were done on 30 patients, three of the patients having the procedure done on two occasions. In every patient some increased increment of growth was obtained, but in only three patients was the amount of growth obtained sufficient to justify the procedure. We have been impressed that in a child below the age of six, with a discrepancy of from one and one-half to two inches, the method described has merit in that the inequality of length can be reduced a small amount, or at least the discrepancy can be kept from becoming greater until such time as the child is old enough for an arrest, or shortening operation. In any study of growth stimulation, clinical measurements of leg lengths are too inaccurate to be relied upon for evaluation purposes. We use a method of x-ray measurement, which permits measurement of the tibia and femur separately, as well as permitting measurement of the total length of each leg. I feel very strongly that any evaluation of a stimulation or an arresting procedure must be dependent upon very accurate x-ray measurements of leg lengths, and not be dependent upon the unavoidable human error of clinical measurement.

Dr. Montgomery is to be commended for reporting a method of growth stimulation which demonstrates that an accurate, honest appraisal of the results obtained, does not justify such a procedure except in a very few instances where it may be combined with another procedure such as relaxation of a tight iliotibial band. It has not been my impression that the implanted ivory chips have been very absorbable as we can demonstrate remnants of the ivory in the medullary canals as late as three years afterwards. I am not in agreement with those who state that immobilization of the part with resultant disuse atrophy producing a state of passive hyperemia, is desirable for epiphyseal growth; rather I believe, that resuming normal activities and weight-bearing as rapidly as possible is a desirable stimulus for increased blood flow to the distal femoral and proximal tibial epiphyses. The reported work on the stimulation of bone growth by the production of an arteriovenous fistula is certainly confirmatory evidence that an increased blood supply to an epiphysis will produce acceleration of growth. Those of us interested in this problem must now direct our efforts to devise some method to maintain an increased blood supply to the epiphysis to maintain the acceleration of growth.

I enjoyed Dr. Montgomery's paper very much, and feel that he is to be commended for the reporting of negative results on an investigative procedure, as these negative reports are many times of greater value than the reporting of glowing clinical achievements.

Dr. Richard H. Eppright, Houston, Tex. I would certainly like to thank Dr. Montgomery for the preparation and presentation of this excellent paper.

I have very little to disagree with what he has presented. My own experience has been limited to elevating the metaphyseal periosteum adjacent to the epiphyseal line. This has been disappointing in that the effectiveness seems to be limited to a three to four month period after which growth returns to its preoperative rate, leaving at most a minimal increase in length. Sufficient repetitions of this type of procedure to produce a desired increase in length are usually not feasible.

It is my understanding that Professor Trueta has abandoned the use of beef bone in the medullary canal in attempts to produce epiphyseal stimulation.

Although epiphyseal stapling and arrest have given excellent results, the search for a satisfactory type of epiphyseal stimulation procedure should be continued because of its need in our armamentarium in treating inequality of leg lengths.

Pancreatic Cysts: A Review of Twenty-Three Cases*

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This is a review of a relatively rare condition, offering a discussion of the pathogenesis, clinical picture and management of the disease.

THE ENTIRE PROBLEM OF PANCREATIC CYSTS has been a subject of confusion to the practitioner of general surgery who is never called on to see or treat any sizable number of these disorders during his entire period of surgical practice. Pancreatic cysts are a relatively rare condition compared to the more frequent ovarian cysts and many gastrointestinal neoplasms, but some specific knowledge of their character, cause, occurrence, and management should be included in the armamentarium of any surgeon who accepts the responsibility of opening the abdominal cavity. That this is true is shown most graphically in a case reported by Mendlebaum[1] who operated upon a pregnant woman with a supposed coexisting ovarian cyst and who proved to have, instead, a coexisting pancreatic cyst.

One of the factors which has contributed to the confusion concerning these tumors is the multiplicity of classifications which have been presented. As a simple working basis there are two types of cysts: *true cysts* and *false*, or *pseudocysts*. The true cysts have originally an epithelial lining and are filled with some of the pancreatic secretions. These may be either retention cysts, cystadenomas, or cystadenocarcinomas. Quite rarely seen are parasitic or dermoid cysts of the pancreas. The false, or pseudocysts of the pancreas, are the result of some disruption in continuity of the pancreatic tissue and a resulting extravasation of pancreatic secretions into the peritoneal cavity or retroperitoneal space. This paper is a report on 23 patients having pancreatic cysts who were operated upon at the Vanderbilt University Hospital or Thayer Veterans Administration Hospital.

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Clinical Material

As can be seen from table 1 there were only 3 true cysts in this series of 23 patients. Although two of these were apparently benign in the beginning, after periods of two months and 9 years, respectively, these patients were seen again, and it was found that the tumors were at that time malignant. The third patient had a cystadenocarcinoma at the time of her original examination and operation.

The remaining 20 cases were all instances of so-called false, or pseudocysts of the pancreas. These were due to a variety of causes. The majority were the result of a severe and fulminating pancreatitis with pancreatic necrosis and resultant extravasation of pancreatic enzymes with pseudocysts formation. Those which are listed as due to operative trauma, as against blunt trauma, were in patients who had deep-seated peptic ulceration with erosion of the head of the pancreas. When gastric resection was carried out a denuded area of pancreas was left, and from this the original extravasation took place. This is not an uncommon occurrence although it has not been seen often in these two hospitals. It has been generally accepted as one of the major causes of death after gastric resection for duodenal ulcer of the posterior wall. In two patients in this group there also were demonstrable pancreatic calculi, but it

TABLE 1

TYPE OF PANCREATIC CYST

True Cysts		3
Cystadenocarcinoma	3 (2*)	
Cystadenoma	2*	
False Cysts		20
Due to blunt trauma	6	
Following acute pancreatitis	10	
Due to operative trauma	2	
Other	2	

*Later were malignant and are counted in both categories.

TABLE 2

SYMPTOMS

	Patients With	*Patients Without*
Pain	23	0
Jaundice	3	20
Mass	12	11

is our feeling that such calculi are the result of repeated episodes of pancreatitis rather than the cause of these episodes.

Symptomatology

The various types of cysts present essentially the same symptoms except for differences which result from the causative agents such as trauma, pancreatitis, and the like. Essentially these manifestations are pain, a mass, and, in some instances, jaundice. The relative incidence of these findings is given in table 2. It may be seen that though jaundice does occur occasionally it is the least common of the symptoms. The majority of these patients had noted an abdominal mass. Without exception they had had pain of some type. The duration of the pain prior to the time of operation varied from two years in one individual to two days in another. The patient having the pain for two years was found to have a cystadenocarcinoma, and the patient having only two days of pain had this following blunt trauma to the left upper abdomen received in an automobile accident. The pain was variable in character. It was usually epigastric with radiation through to the back (10 patients) but also was localized in the right upper quadrant in 4 cases, and the left upper quadrant in 6 cases. In one individual the pain was confined to the right shoulder entirely, and in another there was pain only of a pleuritic character in the left lower chest.

TABLE 3

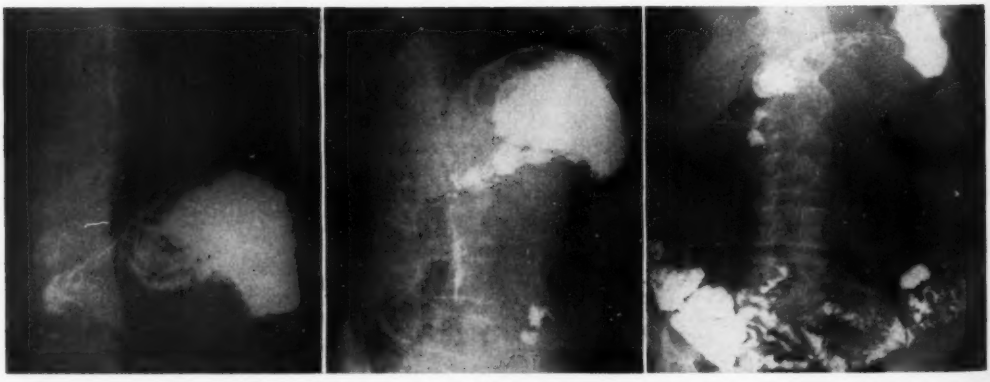
FINDINGS ON INITIAL EVALUATION

	Patients With	*Patients Without*	*Not Checked*
Abdominal mass	21	2	0
X-ray changes	14	5	4
Serum amylase elevation	9	14	0
Amylase activity in cyst fluid	12	0	11
Diabetes mellitus	3	20	0

Diagnosis

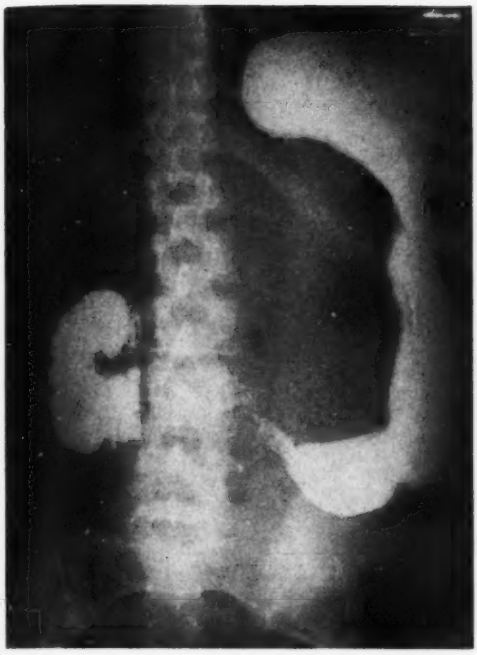
At the time of the original evaluation for pancreatic cyst, the most consistent findings were a mass, a demonstrable deformity of the upper gastrointestinal tract on x-ray examination, and in some instances an elevated serum amylase (Table 3). Three patients had the diagnosis of diabetes mellitus made at the time of admission. A serum amylase of more than 200 Somogyi units was accepted as an elevation, and there were 9 patients who had such a change, the highest elevation being 592 Somogyi units in a patient having drainage from an ulcer base in the pancreas. None of the patients in the true cyst group had an elevated serum amylase. In several instances the cysts were evacuated in the operating room and the fluid in the cyst was checked for amylase activity. The lowest activity was 442 Somogyi units and the highest was 24,000

FIG. 1



Three views of a pancreatic cyst in the head and proximal body of the pancreas. (A) Upward displacement of the stomach. (B) Anterior and upward displacement of the stomach as seen on lateral view. (C) The widened duodenal loop and downward displacement of jejunum and ileum.

FIG. 2



A pancreatic cyst pressing on the lesser curvature of the stomach.

units. None of the fluids from the group of true cysts was included in the series checked for amylase activity.

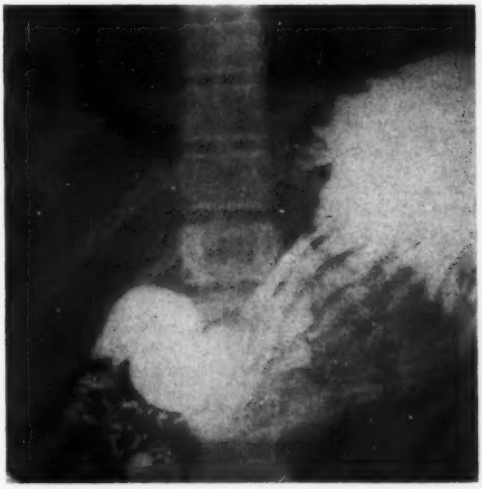
The diagnostic test of most consistent value is the upper gastrointestinal examination by means of the barium meal (Figs. 1 to 4). In 14 patients the mass was accurately located by the deformity produced in the stomach, duodenum, and jejunum. In 6 of these the impression of the radiologist was "pancreatic cyst." The deformity varied with the location of the cyst. Cysts in the body and tail of the pancreas displaced the stomach to the right and anteriorly, while the cysts of the head and adjacent body produced a marked widening of the duodenal loop between the first and third portions of the duodenum.

Treatment

The surgical management of pancreatic cysts has been a matter for extensive discussion in the recent past. Cystojejunostomy, with or without a Roux-en-Y procedure, or cystogastrostomy are technics for internal drainage which have been widely advocated. A total of 27 operations have been done on the 23 patients in this series (Table 4). External drainage has been accomplished either by direct suture of the cyst wall to the skin, or by multiple drains to the skin surface. In one instance a concomitant vagotomy and in another a division of the sphincter of Oddi was carried out at the time of drainage. Of the two patients who were not drained primarily, one was treated by a resection of the distal half of the pancreas (Case 1), and the other by a Roux-en-Y cystojejunostomy. The secondary procedures which proved necessary were a cystojejunostomy for a recurrent cyst, a vagotomy for persistent drainage in one case, a secondary excision for another such instance, and a reopening of one of the patients who had a cystadenoma which later showed evidences of malignancy. There is no known instance, other than these listed, where the patient has had a recurrence of symptoms or has had persistent significant drainage. The one patient (Case 2) who had a true cyst for 9 years did have continued drainage for this period of time which required the constant wearing of a dressing.

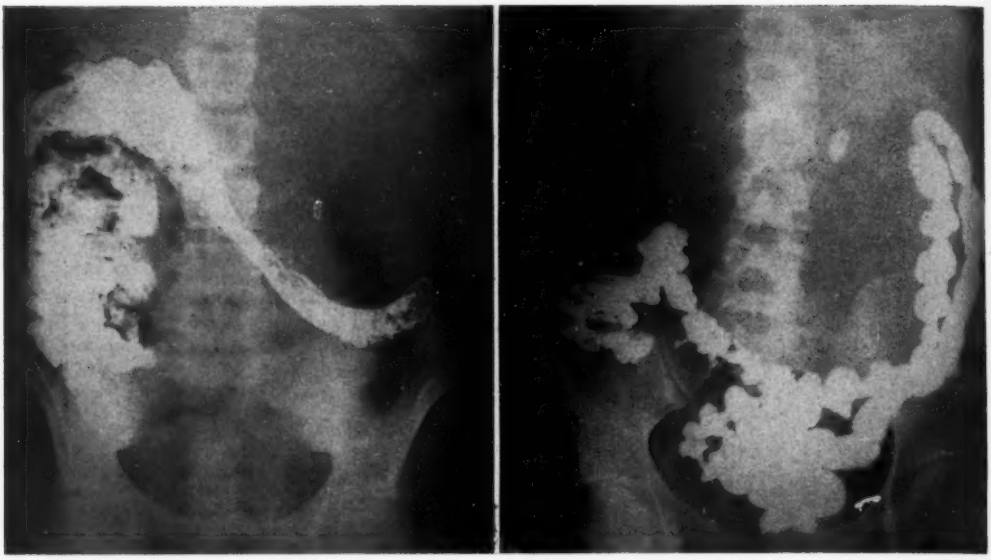
In this series of cases there were three postoperative deaths. One was due to the aspiration of vomitus on the ninth postoperative day after a successful convalescence up until

FIG. 3



The type of pancreatic cyst which may be treated by cystogastrostomy. The flattening of the stomach along the anterior wall of the cyst is shown by the prominence of the gastric rugal markings over the cyst.

FIG. 4



Displacement of colon as shown by barium enema. (A) Case 1. (B) Cyst of the midbody of the pancreas.

that time. The second was a patient having in addition to the pancreatic cyst a carcinoma of the colon at the time of the original exploration. The carcinoma could not be removed, and death ensued on the fourteenth postoperative day from a perforation of this lesion. The third death occured as a result of acute and chronic pyelonephritis with uremia in a patient who had undergone a cystojejunostomy of the Roux-en-Y type.

There were two patients in this series who are of unusual interest because of some facet of their illness. These two cases are reported briefly.

Case 1. (V. U. H. 105203). An 18 year old white man was admitted to the Surgical Service of the Vanderbilt University Hospital in February, 1940. He gave a history of being hit 8 months before, by a large log, which struck him on his left anterior chest and rolled down over his abdomen. He was taken to another hospital and was said to have suffered a fracture of both rami of his pubis and a rupture of his left lung with pneumothorax. He was treated by bed rest for 6 weeks and had gotten along very well. Five months before admission he noticed a soft swelling in his left upper abdomen which would persist for a few days and then disappear spontaneously, leaving some residual abdominal soreness. This had recurred with some regularity every week, lasting 2 or 3 days and then disappearing only to recur again.

TABLE 4

SURGICAL TREATMENT

Drainage		21
Internal		
Roux-en-Y cystojejunostomy	2*	
External		
Simple drainage	8	
Marsupialization	11	
Excision		4
Primary	3	
Secondary	1*	

*Figures include one secondary operation.

X-ray examination of the gastrointestinal tract revealed the stomach to be displaced anteriorly and slightly upward, and the small intestine downward and to the right (Fig. 4, A).

It was decided to explore his abdomen. However, on the night before exploration the mass disappeared, and at operation there was no abnormality of significance other than some 600 cc. of brownish fluid in the free peritoneal cavity. Following operation, on the twelfth day, the mass recurred exactly as before and he was again explored. At this time a large thin walled cyst containing 3,000 cc. of clear fluid was found. This cyst arose from the center of the pancreas which was found to be actually divided into two parts. The cyst and distal half of the pancreas were removed and the abdomen closed without drainage. He recovered uneventfully from the procedure and is now alive and well.

Apparently, when the log had rolled over his abdomen 8 months before admission it had severed the body of the pancreas, and this had drained spontaneously at intervals into the free peritoneal cavity.

Case 2. (V. U. H. 145106). A 45 year old colored

woman was admitted to the Gynecologic Service of Vanderbilt University Hospital in July, 1945. She was admitted with the clinical impression of ovarian cyst.

Roentgenologic examination revealed, however, that the displacement of the intra-abdominal viscera was exactly the opposite of what might be expected from an ovarian tumor, and the diagnosis was changed to an upper abdominal mass, probably a cyst. At operation a 12 by 14 by 12 inch cystic mass was found which incorporated within its substance the celiac vessels. The cyst was evacuated and partially excised. The remaining wall was sewn to the skin, and a marsupialization procedure done. The patient had a relatively uneventful postoperative course for two weeks and then developed signs of small bowel obstruction. She was re-explored and some adhesions freed 26 days after her original procedure. She did well after this second operation and was discharged on her forty-fourth hospital day.

This patient was observed at intervals until 1950, when she stopped coming to the Surgical Out-Patient Department, although she had continued to drain from the time of her marsupialization until she was last seen. In September, 1954, nine years after the original drainage procedure, she returned with a history of having noted for two months some little "knots" around the draining sinus. These had become progressively larger and, although she had only a serous drainage from the site of marsupialization during the preceding 9 years, for this two month period she had had bloody drainage from the tract. At examination a firm raised ulcerated draining mass 12 cm. in size was present in her left upper quadrant; around this were 14 pigmented hard areas, 1 cm. in size. A biopsy of one of these established the diagnosis of adenocarcinoma.

Conclusion

The most common type of pancreatic cyst encountered in this and most other reported series is the pseudocyst, usually resulting from pancreatitis or blunt trauma. True cysts of the pancreas are rare and when found are frequently malignant cystadenocarcinomas. In the series of patients treated at the Vanderbilt University and Thayer Veterans Administration Hospitals simple external drainage, with or without formal marsupialization, has been an effective and safe operative technic. Cysto-enterostomy should be reserved, in our opinion, for those patients having true cysts which cannot be excised, since it is these individuals who seemingly continue to drain for long periods of time.

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Discussion (Abstract)

Dr. Henry M. Carney, Texarkana, Tex. I am grateful to Dr. Foster* for giving this scholarly presentation of this subject. You will be glad to know that any discussion of this subject, if it is in any way comparable to the experience of one surgeon, will of necessity be short.

I think it is extremely important, however, that this subject be brought to us because the greatest errors, that are made in surgery are made in the conditions which we encounter very infrequently. Probably most of the pancreatic cysts encountered are met by surgeons for the first time, and without any preparation as to what to do with them.

In our hospital, fortunately or unfortunately, we have had only two in the past five years. Both followed long periods of a history of pancreatitis, both recovered after being treated by external drainage.

I had one patient that corresponded very closely to Dr. Foster's patient, in which the pancreas was completely divided. This patient was a logger and was struck in the abdomen by a cant hook. When the log tumbled down and hit it, it struck him in the abdomen. Fortunately, we explored the abdomen immediately and drained it. He had developed a pancreatic fistula but by suction he recovered.

I have learned two things from this discussion and by some review of the literature. One of these I do not believe was mentioned by the essayists. Under no circumstance should one attempt to remove these cysts. That has been attempted in a few cases and most of the time it has been disastrous. There is an obvious reason for this. These cysts are thick-walled, and are intimately adherent to vital structures of which there are a large number in the upper abdomen. Excision usually results in a tear of the common bile duct, or some large vein or artery.

The only point in which I might differ a little with the author is in regard to the treatment. I do not have any long series of cases to substantiate my viewpoint. The ones that we have had have been drained externally. If we had a large pseudocyst of the pancreas and were sure of our diagnosis, substantiated by x-ray findings, I believe it would be good reason to drain the secretions of the pancreas into the gastrointestinal tract where they belong. I believe it is significant that the average patient drains for five and one-half months externally, and that is a marked inconvenience. If they are to be drained into the gastrointestinal tract, the stomach would be the place of choice because most cysts are intimately adherent to the posterior wall of the stomach.

*This paper was read at the Houston meeting by Dr. John Foster, Nashville, Tenn.

Electromyography in Clinical Practice*

HARRY W. MIMS, M.D., *Charleston, S. C.*

This technic has a place in the differential diagnosis of lesions of neurologic origin and of primary diseases of muscle. It may be helpful in prognosis.

Technic

THE DEMONSTRATION OF DENERVATION OF SKELETAL MUSCLES in lower motor neuron disease is the chief value of electromyography in clinical practice. Basically the apparatus required for such an examination consists of receiving electrodes, which may be of the percutaneous type that are taped to the skin over the muscle being tested, or needle electrodes that are inserted into the muscle itself. The needles must be properly insulated. A ground electrode is strapped to a convenient adjacent area. Electrode paste is applied to the ground electrode and to skin electrodes when these are used. The electrical action potentials from the muscle are then picked up by the receiving electrode, transmitted to a high gain amplifier, and thence to an oscilloscope where their wave form can be seen. At the same time, they may be led into a loudspeaker system, permitting audible as well as visual examination of the electrical activity of the skeletal muscle. Still or motion pictures of the screen and tape recordings of the sound permit permanent records to be made of every case. Choice of electrodes is important. For diagnosis of lower motor neuron injury or disease, needle electrodes are essential, as denervation voltages cannot be demonstrated by skin electrodes.

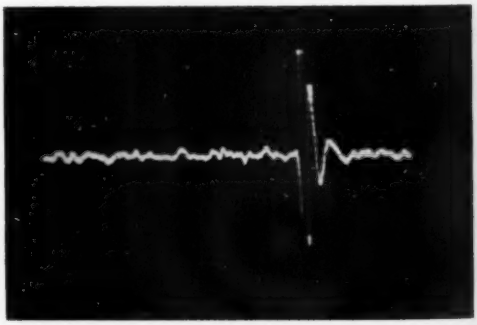
Properly prepared needles can pick up the activity from single motor units. A motor unit consists of the muscle fibers supplied by a single anterior horn cell and its axon. The cell, axon, and muscle fibers combined make up the individual unit. The number of fibers per unit has been estimated to be 100 to 200.[1]

Types of Muscular Activity

Normal skeletal muscle at rest shows *no electrical activity*. When the muscle is voluntarily contracted, there appears on the oscilloscope potentials which follow a definite pattern in wave form, amplitude, duration and frequency (Fig. 1). The sound of this activity over the speaker is also typical. There is no activity either visible or audible until contraction occurs, and it then disappears after relaxation of the muscle. The wave forms of normal motor units are usually diphasic but may be mono- or triphasic. Magnitute is 500 to 2,000 microvolts, duration 2 to 10 milliseconds, frequency 5 to 30 per second.[2] Frequency varies with the degree of voluntary contraction effort. These potentials have a distinct tapping sound of moderate pitch.

Denervation of skeletal muscle is evidenced by *fibrillation*, which is a fine, rhythmic contraction occurring involuntarily. Fibrillation is not visible through the skin, and it cannot be demonstrated by percutaneous electrodes. It should not be confused with the coarse, visible involuntary twitching of skeletal muscle, frequently seen in certain nervous diseases and occasionally in the normal. This type of muscle activity is called fasciculation and will be discussed later. Since fibrillation contractions are involuntary, they occur when the muscle is at rest but may increase during any voluntary activity that is possible. Fibrillation is pathognomic of denervation. Al-

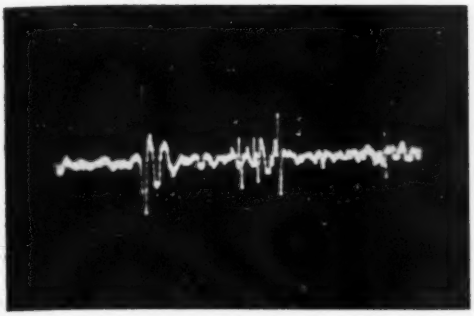
FIG. 1



Normal voltage.

*Read before the Section on Physical Medicine and Rehabilitation, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

FIG. 2

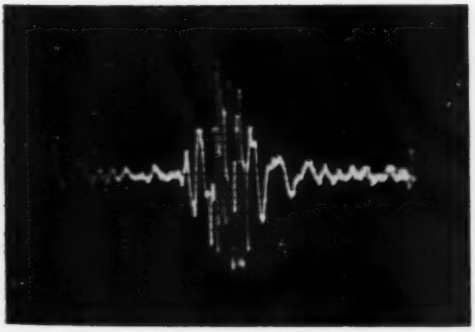


Fibrillation voltages.

though voluntary contraction may increase the number of these voltage potentials, they should always be demonstrated with the muscle at rest before it is said to be denervated. The small normal action potentials seen in primary muscle disease may be confused with fibrillation, but they do not occur at rest. Fibrillation may not be exhibited by a muscle for as long as 21 days after the onset of disease or injury, since nerve degeneration has to occur first. Fibrillation potentials are usually mono- or diphasic, with a magnitude of 10 to 100 microvolts, duration 1 to 2 milliseconds, and frequency 2 to 30 per second[2] (Fig. 2). They have a highpitched frying sound, when found in large numbers, and are easily distinguished from normal potentials by sound as well as visual characteristics.

Another type of wave form is the *complex* or *polyphasic* motor unit voltage. Being polyphasic, they exhibit many spikes,—at least four or more. Magnitude is 20 to 1,200 microvolts or more, duration 3 to 20 milliseconds, frequency 5 to 30 per second[2] (Fig. 3). They have a coarse, jumbled, low pitched sound. Polyphasic voltages occur on voluntary effort when there is denervation or reinnervation taking place. They may be found when the site of the lesion is anywhere in the lower motor neuron. During early denervation polyphasic activity may be abundant, giving away to fibrillation as the process becomes more complete. It then reappears if reinnervation occurs with fibrillation decreasing. Polyphasic voltages may be demonstrable when the patient attempts movement before there is any visible evidence of muscle contraction. In a peripheral nerve injury, for example, their appearance in increasing numbers on repeated examination is a favorable prognostic sign. Polyphasic voltages are often seen with fibrillation indicating partial but incomplete denervation. When found occasionally with no evidence of fibrillation they are not of clinical significance and should be disregarded.[3]

FIG. 3



Complex voltages.

The fourth type of potential is that of *fasciculation*, which electromyographically is similar to polyphasic voltages. Fasciculation is a coarse, visible twitching of skeletal muscle. It occurs involuntarily with the muscle supposedly at rest and is thus distinguished from the polyphasic activity occurring on voluntary effort. Fasciculation is due to an irritation of the lower motor neuron, and though frequently seen in such diseases as amyotrophic lateral sclerosis, may also occur in the normal individual. It must be interpreted in relation to other clinical findings and occurring alone does not form a basis for the diagnosis of disease.

Various other wave forms have been described which may have some meaning, especially when interpreted along with other findings. However, for usual clinical practice, the four mentioned above are all that need be discussed. These four types of action potentials usually are easily identified by their sound and gross appearance on the oscilloscope. If the findings are vague, the examination probably should be repeated or other means of diagnosis used.

If the basic physiologic principles of electromyography are understood, its clinical applications are fairly simple and clear-cut. Fibrillation occurs only when there is destruc-

tion in the lower motor neuron, and is the one conclusive finding in electromyographic examination. It is not found in upper motor neuron lesions, primary muscle diseases, nor in old denervated muscle that has undergone fibrosis. When fibrillation is not found, it does not necessarily rule out the presence of denervation, since scattered denervated fibers may not be touched by needle electrodes. This emphasizes the need of detailed, careful examination. If a careful examination is done, not only is fibrillation more apt to be found if it is present, but also a negative finding then carries much more authority.

Use of Electromyography

The electromyogram is especially valuable in the differentiation of lower motor neuron and primary muscle disease. These two types of disease are sometimes impossible to differentiate clinically, and the finding of fibrillation identifies the lower motor neuron as the site of involvement. In such conditions as muscular dystrophy and myasthenia gravis, the potentials are normal except for the decreased amplitude and rapid fading away when sustained contraction is attempted. It has already been mentioned that the potentials may be so small as to give the appearance of fibrillation, but are distinguished by the fact that they do not occur at rest.

In poliomyelitis, widespread evidence of denervation may be found since the involvement in this disease is typically spotty and not segmental in type. Areas of fibrillation may be found in muscles that show little or no clinical weakness. In peripheral nerve injuries, electromyographic findings will be confined to the areas supplied by the involved nerve. This applies also to interference in the nerve root such as occurs with ruptured intervertebral discs. In other words, emphasis is placed on those areas where abnormal findings are most likely to be encountered. It goes almost without saying that to properly do an electromyographic examination and to interpret the results requires the same knowledge of anatomy, physiology, and pathology as any other clinical or laboratory procedure.

Several areas of a muscle should be sampled, and to do this the muscle is arbitrarily divided into proximal, middle, and distal one-thirds. After the needle is inserted, it may then be moved around a circle without withdrawal through the skin. This permits three or four samplings with one skin puncture. Therefore, for examining a muscle divided into three parts, only three punctures are needed to sample a total of 12 to 16 different areas. In small muscles, one or two punctures may be sufficient.

Although primarily thought of as a diagnostic instrument, the electromyogram may be used for treatment as an aid in muscle reeducation when it is difficult for a patient to learn to use a specific muscle that has undergone a change in normal status for one reason or another. This is especially true in those recovering from poliomyelitis, or following muscle transfers where a muscle must then perform a different function from its normal one. Although the nerve is intact the subject cannot get a good muscle contraction. Connecting such a muscle to the electromyograph with skin electrodes enables one to see and hear the potentials each time the proper movement is made and voluntary control is learned much more quickly.

Summary

The greatest contribution of the electromyogram is that it affords a means of conclusively demonstrating denervation of skeletal muscle, as shown by fibrillation. Properly utilized and understood it also offers supporting evidence in the diagnosis and prognosis of many neuromuscular diseases, and has some use as a treatment aid. However, in no sense does it take the place of a good physical examination, nor of simpler methods of electrical testing, such as chronaxie.

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Discussion (Abstract)

Dr. T. H. Lundstrom, Mountain Home, Tenn. Electromyography is a valuable addition to our various diagnostic aids. Dr. Mims has presented a very concise paper on its use in clinical practice, and has stressed its primary usefulness in demonstrating denervation fibrillation as conclusive evidence of lower motor neuron injury or disease. By the use of electromyography it is possible to differentiate between normal muscle, denervated muscle of various degree, and

primary muscular disease. In this respect the use of electromyography, in the diagnosis and prognosis of neuromuscular disease involving the lower motor neuron, is comparable to the use of electrocardiography in cardiology. It will, no doubt, be used more and more in the future as more doctors become proficient in its application.

As with other diagnostic modalities the ability to use electromyography to its fullest degree grows with practice. What at first appears to be very confusing gradually becomes clear and meaningful. Thus, to begin with it is difficult to recognize with certainty the various wave forms on the oscilloscope. Dr. Mims has said that each wave form has its characteristic sound which identifies it. This is important since the various potentials are often more easily recognized by their sound than by their wave form.

The need of detailed, careful examination has been emphasized. In this connection I should like to point out the value of carefully noticing the sound which is elicited as the needle electrode is inserted. When the needle is inserted into a normal muscle only a few action potentials of short duration will be noted. On the other hand, if the muscle has lost its nerve supply it becomes hyperirritable and the mechanical stimulation of the needle, as it is inserted, causes a prolonged activity which is first manifested by positive sharp waves sounding like distant thunder, followed by repetitive fibrillary spikes which sound like a rain-shower, and then ending in fibrillation potentials with a sound like that of fine rain falling on a tin roof.[3] Thus, by noticing the activity upon inserting the needle in the muscle to be explored, it may be possible to make definite conclusions as to whether the muscle is normal or abnormal, thereby eliminating unnecessary skin punctures.

There is one confusing wave form which I should like to call to your attention. It is the so-called pseudo-fibrillation potential. These are potentials which are generated when the needle electrode happens to come in contact with a nerve fiber within the muscle. Instead of being positive fibrillation potentials of the usual denervation type, these are usually negative fibrillation-like potentials. They are recognized by the facts that the patient, as a rule, will complain of pain at the point of the needle, and that their activity ceases abruptly on moving the needle very slightly, away from the nerve.

It may also be mentioned at this time that in order to eliminate outside electrical interference which is constantly present in any department of physical medicine, it is practically a necessity to have all testing done in a copper-screened room.

Again, I should like to emphasize the usefulness of electromyography in ruling out such conditions as hysteria and malingering, also in differentiating between disuse atrophy, muscular atrophies and the myopathies, and in peripheral nerve injuries and spinal nerve root compressions.

Dr. Howard L. Schnur, Houston, Tex. I wish to compliment Dr. Mims for the lucid manner in which he has summarized the essential features of electromyography, the equipment, the basic physiologic principles, and the clinical applications. I find myself in agreement with him on most points. I endorse his conclusion that the electromyogram does not take the place of a good history and neurologic examination, but that if properly carried out and interpreted, it can offer valuable objective evidence in the diagnosis and prognosis of many neuro-muscular diseases.

In his paper, Dr. Mims lists several areas in which E.M.G. evidence may be helpful in diagnosis. For the purpose of review, I shall repeat them: (1) the differentiation of lower motor neuron and upper motor neuron disease; (2) the differential diagnosis between lower motor neuron disease and primary muscle disease, such as the dystrophies and the myotonias; (3) poliomyelitis; (4) ruptured intervertebral disk, and (5) peripheral nerve injuries.

It is in this latter group of peripheral nerve injuries, that we at the Houston Veterans Administration Hospital find the greatest use for the electromyograph. With it we can localize the lesion, estimate the degree of damage, and follow the course of regeneration or, if progress is halted, refer the patient to the neurosurgeon at the earliest possible time, before irreversible changes have occurred in the muscle.

To conclude, with Dr. Mims, I feel that detailed, careful electromyography by physicians well-trained in neuromuscular anatomy and physiology can offer valuable diagnostic and prognostic information to our colleagues.

Dr. Louis Leavitt, Houston, Tex. I wish to compliment Dr. Mims for the lucid manner in which he has summarized the essential features of electromyography. Dr. Mims, do you take movies of the oscilloscope, and if so, have you managed to get synchronization between sound and vision?

Dr. Mims (Closing). As Dr. Lundstrom pointed out there are certain things that you should look for on needle insertion. I did not mention that particularly because I still feel although one does find some abnormality on insertion of the needle and one does get activity, one should wait until that subsides before drawing a final conclusion. And although it is an aid, I still feel it has to be correlated with the rest of the clinical findings, but it is a valuable part of the examination. One should always observe and listen for the potentials during the needle insertion.

In answer to Dr. Leavitt's question, I do not take movies of the oscilloscope.

Place of Trichlorethylene in Obstetrical and Anesthetic Practice*

L. W. FABIAN, M.D., C. R. STEPHEN, M.D.,
and M. BOURGEOIS-GAVARDIN, M.D.,† *Durham, N. C.*

This anesthetic has common use in practice for short anesthesia. It has been shown that there may be dangers associated with its use in closed circuit anesthesia, if such is continued after the use of nonbreathing inhalers.

PRIOR TO THE ONSET OF WORLD WAR I, trichlorethylene had attained a reputation of note as an excellent solvent and not until increased production demands arose was any notice taken of the drug's analgesic properties. As a result of the occasional incidence of paresis of the trigeminal nerve in workers exposed to trichlorethylene during its manufacture, Plessner, in 1916,[1] suggested its use as an analgesic and therapeutic drug for trigeminal neuralgia. Others took up this study (Glaser,[2] Oljenick[3]) and more extensive pharmacologic investigation was begun. Krantz and Carr (1935)[4] demonstrated the generalized analgesic effects of the drug and disproved the theory of specificity of action on the trigeminal nerve. Sporadic reports of successful trials in producing surgical anesthesia were made, Jackson[5] and Striker[6] being major contributors in the earlier clinical investigations. Studies concerning the metabolism of trichlorethylene to trichlorethanol and trichloracetic acid were reported by Butler.[7]

Greatest impetus to the use of the drug was given during World War II when the demands arose for a potent, easily available and transportable and nonflammable anesthetic became great. Hewer[8] in England is credited with the investigative work which led to the present popularity of trichlorethylene. Through his work, methods of purification and stabilization were developed. These methods were necessary before general release of the drug for medical use since the commercial product contains about 5 per cent impurities. Dichloracetyl chloride and hydrogen chloride were isolated from the commercial solvent and it was noted that phosgene (carbonyl chloride) was detectable during vaporization of the compound. The danger of provoking serious cutaneous and pulmonary irritations with such impurities was already well known in the case of phosgene since it had been used as a war gas of the lung irritant type during World War I (Table 1).

The preparation currently used in analgesia and anesthesia is highly purified trichlorethylene and marketed as Trilene and Trimar. Highly stable under ordinary circumstances, the drug can nevertheless be decomposed to some extent by exposure to excessive heat and light or to alkali. Contact of the vapor with highly alkaline substance becomes a clinical problem in that the halogenated derivatives mentioned above may be produced by using trichlorethylene in closed circuit anesthesia. Carbon dioxide absorbents such as soda lime and Baralyme serve as the alkaline medium in such a system.

TABLE 1

PHYSIOLOGIC RESPONSES TO VARIOUS CONCENTRATIONS OF SOME COMMON GASES AND VAPORS* PER CENT BY VOLUME IN AIR

Vapor or Gas	*Rapidly fatal to most animals*	*Dangerous in 30-60 minutes*	*Maximum amount for 60 minutes with no serious disturbances*	*Slight symptoms after prolonged exposure. (Max. amt.)*
	0.02			
Phosgene	0.05	0.0025	.....	0.0001
		0.004		
Chlorine	0.10	0.006	0.0004	0.0001
Hydrogen Chloride	0.20 0.5	0.15 0.2	0.005 0.02	0.01 0.001
Carbon Monoxide	0.5 1.5	0.2 0.3	0.05 0.10	0.04 0.05

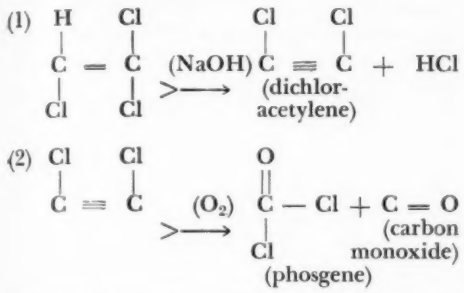
*From Handbook of Chemistry and Physics, Lange 1946, 6th Edition, Page 1660.

*Read before the Section on Anesthesiology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Division of Anesthesia, Duke University Hospital and School of Medicine, Durham, N. C.

Supported in part by a grant from Ayerst Laboratories, New York, N. Y.

The chemical reaction involved in the decomposition of trichlorethylene occurs in two stages as represented below:



Further reference to the clinical significance of this reaction will be made presently.

Methods of Administration

Triclorethylene is vaporized for analgesic or anesthetic purposes by one of two methods. For production of analgesia, a specially devised nonbreathing inhaler is utilized and is of value in the fields of obstetrics and minor surgery. The principle of this method involves drawing air through a metal enclosed wick which has been saturated with trichlorethylene, the vapor passing to a face mask and to the patient. The unit is simple, practical and quite effective in providing a means of self-administered analgesia. Vapor concentrations vary according to the scale setting on the instrument.[9] This device has been used primarily for producing analgesia during labor in obstetrics.[10] Urologic procedures of minor nature, painful burn dressings,[11] simple incision and drainage procedures and minor dental procedures[12] have also been performed successfully using this type of analgesia.

For anesthetic procedures, the drug is generally volatilized by allowing certain gases such as nitrous oxide and oxygen to pass *over* (not bubble through) trichlorethylene, using an anesthetic machine. The supplementary analgesia produced by nitrous oxide aids in the achievement of light surgical anesthesia. Muscle relaxant drugs are usually required as adjuncts to this method of anesthesia if the surgical procedure demands laxity of skeletal muscle in the involved area. The system used for this purpose may be either nonrebreathing or partial rebreathing with high flows of gases. An absorber is used in the circuit. Nonrebreathing is preferred.

During the past 15 years several cases of postanesthetic nerve pareses and fatalities have been reported as a result of using trichlorethylene in closed circuit anesthesia.[13,14] These reports indicate the soda lime used in these cases had been previously exposed to trichlorethylene vapor and imply that fresh soda lime would not have imposed such a hazard even if exposure to trichlorethylene vapor occurred for a short time. The hazard of toxic decomposition, then, apparently increases in proportion to the time of trichlorethylene-alkali contact.

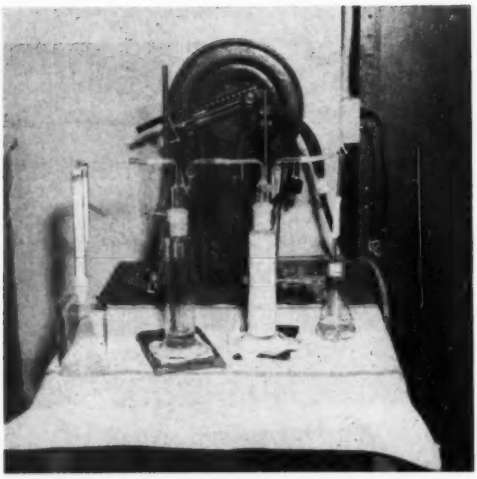
The question now arises concerning the patient who, after using an inhaler for some time, is subjected after a short interval to closed circuit anesthesia. Can this be done safely or should a specific time interval be allowed before pursuing an anesthetic course using an anesthetic machine and carbon dioxide absorption? What is the danger of significant toxic decomposition of the trichlorethylene vapor expired by such a patient if absorption technics are used minutes after the inhaler has been used? In order to obtain more definite answers for these questions, the following objective laboratory investigation was begun.

To ascertain certain associations between chemical decomposition as determined by chemical means and those determined by animal studies, the project was divided into two phases. The former phase is, in part, repetition of work previously reported by Firth and Stuckey.[15] The animal study is believed to be original work and attempts to simulate clinical situations.

Methods of Study

In the chemical phase of this study, an apparatus was devised which enabled us to collect small amounts of the decomposition compounds for general chemical analysis in our own laboratories. The passage of Trilene vapor through soda lime during careful temperature and flow rate controls and the collection of this vapor in special containers for precipitation of unstable halogen compounds presented no small problem. A major concern involved the instability of dichloracetylene which is spontaneously flammable in air or oxygen. To precipitate this compound cupric ammonium nitrate with hydroxylamine hydrochloride (Ilosvay's reagent) was used yielding

FIG. 1



Photograph of equipment used in chemical extraction of vapor to be analyzed.

measurable amounts of cupric acetylide (Fig. 1). Other halogen compounds which had been trapped in the soda lime were detected by titrimetric chloride determination (method of Volhard). These data concern direct vapor-alkali contacts however, and, although pertinent to general usage, are of less direct value in this project. Positive qualitative tests for phosgene and chlorides were obtained only after one hour of such exposure and are important solely in comparing these results with the data obtained in the animal studies.

The animal phase seemed our most important phase; therefore special efforts were made to mimic closely clinical situations. Cardiovascular and respiratory dynamics were observed continuously during this study utilizing an eight channel electroencephalographic recorder with electronic adjuncts as were necessary. Complete studies are presented as obtained from ten such experiments (Fig. 2).

FIG. 2

Photograph of animal experiment in progress showing method of recording physiologic data by electronic means.

Attaching a Duke University inhaler (set at mark 4) to the endotracheal tube exposed the animal to a total of 30 cc. of Trilene (15 cc. per hour) in 2 hours.* During this period room air inhalations were allowed intermittently for 5 of each 15 minutes.

Following the intermittent periods of inhalation of Trilene and room air, an additional period varying from 5 to 60 minutes was allowed for further inhalation of room air. At the end of this period, a "to and fro" cannister charged with 200 grams of Baralyme or soda lime was attached to the endotracheal tube and rebreathing was allowed for one hour (plus or minus 15 minutes). Constant temperature observations were obtained by inserting a thermometer into the cannister where it would be centrally placed in the alkali.

To obtain samples of vapor condensation from the alkali, collections were made in a specially designed vapor trap which was submerged in a cooling mixture of either dry ice and acetone (—90° C.) or liquid nitrogen (—190° C.). This process was carried out in a completely closed system made possible by the use of a Palmer pump through which circulation of a small amount of air could be maintained at a constant rate and volume. The air used in this system had been placed previously in the rebreathing bag interposed in the apparatus. This period consumed an additional hour, thereby allowing a total trichlorethylene-alkali exposure of 2 hours per experiment. Evacuation of the traps at pressures of 20 to 60 mm. Hg. provided less atmospheric air contamination.

Evaluation of the possible increased hazards associated with alkali previously exposed to trichlorethylene was made possible by airtight preservations of the soda lime used in previous experiments and loading future cannisters with this material. Samples of the alkali were preserved on six different occasions thereby allowing each of two animals to be exposed to soda lime which had previously been in contact with trichlorethylene vapor for a total of 4 hours.

*The vapor concentration at this scale setting is about 0.85 per cent and 15 cc. of Trilene should provide 3 to 5 hours of intermittent analgesia.

Analysis of Mass Spectrometric Data

Due to the instability of the halogen derivatives of trichlorethylene complicated by the necessity for pure compounds for calibration of the mass spectrometer, it is difficult at present to give precise concentrations of the ions involved. Many of the ions also possess mass numbers not too dissimilar.

Certain statements can be made regarding application of these data to the clinical use of trichlorethylene (Tables 2, 3 and 4).

First, it should be noted that only in cases where repeated use of the soda lime and/or repeated subjection of the animals to further experiments were significant quantities of hydrogen chloride and dichloracetylene found. Also of importance is the fact that each of these experiments was associated with soda lime which had reached higher temperature ranges (i.e., temperatures above 37° C.).

Secondly, it appears that by lengthening the period of inhalation of room air between the time of abstaining from use of the inhaler and the moment at which circle absorption (closed circuit) anesthesia is begun, the degree of hazard is profoundly decreased.

Thirdly, stabilization of these compounds by loose molecular combination with soda lime seems evident in these studies implying an even further decrease of the hazard in question. The absence of phosgene is quite con-

TABLE 2

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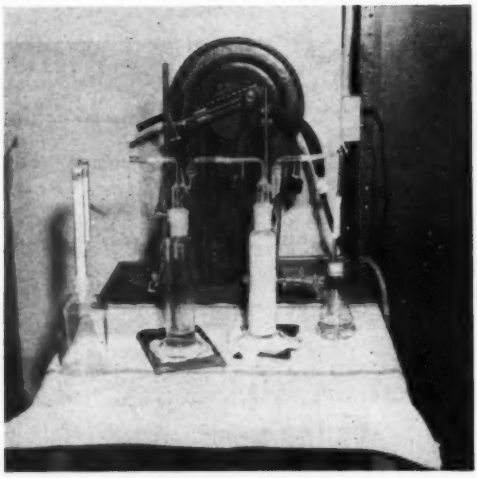
VALUES GIVEN IN MOLES %. LIQUID (L) AND VAPOR (V) PHASES

	Pre-extraction alkali temperature	*Minutes allowed for final room air inhalation*	*Phase*	*HCl*	C_2Cl_2	$COCl_2$	C_2HCl	*Trilene*	*Air*	*Water*	N_2 *&/or* CO	
I	26	5	L	0.2	0.2			5.5	11.0	33.0	48.3	
			V	Trace					91.9	8.1	Trace	
II	43	30	L				0.7		61.5	36.8	1.0	CO_2
			V				0.1		83.3	16.5	0.1	CO_2

FIG. 1



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VALUES GIVEN IN MOLES %. LIQUID (L) AND VAPOR (V) PHASES

	Pre-extraction alkali temperature	*Minutes allowed for final room air inhalation*	*Phase*	*HCl*	C_2Cl_2	$COCl_2$	C_2HCl	*Trilene*	*Air*	*Water*	N_2 &/or CO	
I	26	5	L	0.2	0.2			5.5	11.0	33.0	48.3	
			V	Trace					91.9	8.1	Trace	
II	43	30	L				0.7		61.5	36.8	1.0	CO_2
			V				0.1		83.3	16.5	0.1	CO_2

TABLE 3

MASS SPECTROMETRIC ANALYSES OF VAPOR EXTRACTED FROM SODA LIME FOLLOWING SECOND EXPOSURE TO TRILENE VAPOR (4 Hours)
VALUES GIVEN IN MOLES %. LIQUID (L) AND VAPOR (V) PHASES

	Pre-extraction alkali temperature	*Minutes allowed for final room air inhalation*	*Phase*	*HCl*	C_2Cl_2	$COCl_2$	C_2HCl	*Trilene*	*Air*	*Water*	N_2 &/or *CO*	
I	40	10	L	1.4	1.0			61.4		14.2	36.2	
			V	0.6	0.2			10.3	23.7	63.5	1.7	
II	41	5	L									
			V	0.1	0.1			5.7	94.0	0.1		
III	43	30	L		0.1			1.2	92.2	6.3		
			V					1.4	92.9	5.7	0.1	
IV	43	60	L				13.0		48.1	38.7	0.2	CO_2
			V				0.9		86.5	12.6	0.01	CO_2

spicuous in the animal experimentation phase of this project.

By comparison of the data presented in table 1 with those of tables 2, 3 and 4 it would seem that in certain instances fatal results should have been obtained had these components actually been inhaled by the animals. Apparently this does not present a major problem in the type of technic described therein since none of the animals of this series have expired as a result of the experiments of this project.

By chemical means (e.g., silica gel adsorption of phosgene) following extraction from the soda lime, chlorine fractions have been detected in some abundance. These could be and probably are representative of decomposed phosgene and dichloracetylene. This has been consistent, however, only after several hours of direct vapor-alkali contact.

No substantial evidence of peripheral nerve damage has appeared in any of the animals as observed grossly but pathologic sections have not been undertaken as yet. Indeed no essential abnormalities have appeared in this group of dogs with the exception of one animal which seems generally weaker than the rest. This animal is being observed for further developments indicative of onset and progression of peripheral nerve involvement.

Discussion

Two phases of study were pursued, namely, chemical analyses of the exposed compounds and mass spectrometric analyses of samples obtained through animal experimentation. The latter phase is emphasized due to the pertinence of its clinical correlation. The salient organic and physical chemistry is discussed relative to the clinical problem.

From this investigation, the following observations seem important as bases for answering queries concerning the possibility of toxic decomposition in converting from intermittent analgesia to closed circuit anesthesia.

(1) Of 18 animals used in the study, only one has shown even a remote suggestion of such complications as peripheral nerve pareses.

TABLE 4

MASS SPECTROMETRIC ANALYSES OF VAPOR EXTRACTED FROM SODA LIME FOLLOWING THIRD EXPOSURE TO TRILENE VAPOR (6 Hours)
VALUES GIVEN IN MOLES %. LIQUID (L) AND VAPOR (V) PHASES

	Pre-extraction alkali temperature	*Minutes allowed for final room air inhalation*	*Phase*	*HCl*	C_2Cl_2	$COCl_2$	C_2HCl	*Trilene*	*Air*	*Water*	N_2 &/or *CO*
I	41	5	L	7.8	1.0			64.9		84.6	2.9
			V	0.1	0.2			13.1	80.2	2.7	3.7
II	45	15	L					0.9	12.0	80.4	6.1
			V					0.2	99.5	0.3	
III	44	5	L	0.1	0.1				42.0	50.1	
			V					3.0	95.9	1.0	0.1

This dog has seemed listless and appears to have generalized muscle weakness. Specific nerve paresis is not evident and no other complications are apparent. A relationship to toxic decomposition of trichlorethylene is indeed questionable.

(2) In mass spectrometric analyses, phosgene and free chlorine have been absent in all samples obtained in the animal study. These decomposition products were present in the chemical phase of the investigation wherein long periods of direct Trilene-alkali contact were maintained (Tables 2, 3 and 4).

Six of the ten samples contained dichloracetylene and hydrogen chloride. Two samples contained significant quantities of monochloracetylene. Peaks consistent with nitrogen and/or carbon monoxide were also evident in six samples.

As was expected, the greatest concentrations of halogens were found in those samples obtained from previously used alkali which attained rather high temperatures during the rebreathing period (40° C. or above). It was interesting to note that in extracting soda lime used for the first time with Trilene the temperatures were from 7 to 14° C. lower than those observed with previously exposed alkali.

(3) In those animals allowed to breathe room air for 15 minutes or more before attaching the soda lime cannister, a marked diminution in halogen content was evident in the analysis. This held true even for previously exposed alkali at higher temperatures. It is recommended, therefore, that at least 15 minutes of inhalation of room air be allowed before induction of closed circuit anesthesia.

In view of the consistency of results in the spectrometric analyses and lack of any gross evidence of postanesthetic sequelae, it would appear that conversion from a technic of intermittent self-administered analgesia to one of partial rebreathing or even closed circuit anesthesia offers no hazard relative to formation of toxic substances from a chemical reaction between trichlorethylene and soda lime. The factors considered important in providing this safety are the use of *fresh* soda lime and the utilization of high flow rates of gases and partial rebreathing technics. Short periods of closed circle absorption technics likewise should present no dangers in this respect. Emphasis is placed on the necessity for discarding all soda lime which has been in contact with trichlorethylene so that it will not be used a second time. Decomposition of the loose molecular combination of dichloracetylene or monochloracetylene with soda lime constitutes the real problem in the technics under discussion and this may be avoided by assuring that soda lime exposed to Trilene vapor is never re-used.

Summary

1. A brief resume concerning the clinical use of trichlorethylene anesthesia and analgesia has been presented and emphasis has been placed on the use of nonrebreathing inhalers in obstetrics. Subsequent use of closed circuit anesthesia for these patients has occasionally been necessary and the question of a related trichlorethylene-alkali toxicity has been raised in this aspect.

2. An experimental project has been undertaken in an attempt to ascertain the safety or danger factors involved in the above situation.

3. Laboratory studies designed to simulate such clinical experiences have been carried out and analyses of trichlorethylene vapors extracted from soda lime have been performed.

Acknowledgment

We wish to express sincere gratitude for the aid given us by Dr. Roger Stansfield of the Chemistry Department of Duke University and to Messrs. Joe C. Matthews and James Thompson of our laboratory staff.

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Discussion (Abstract)

Dr. Arthur Keats, Houston, Tex. I am sorry Dr. Fabian did not have more time to present the excellent paper which I had an opportunity to read at leisure. He and his associates have done a beautiful job and a very difficult one. I think we all ought to realize how much work has gone into the laborious chemical analyses required. It is the kind of work I would be proud to have done except that we do not have any mass spectrometers lying around.

We learn from this work that if necessary we can safely put patients who have had trichlorethylene on a closed anesthesia circuit provided we have them breathe room air for a short period first. But at the end of such an anesthetic the soda lime used for this patient must be discarded because of the later production of toxic products. If we must throw out the soda lime each time, we probably will not be using this technic very often since we would soon be ordering soda lime by the carload.

We also learn that it is inadvisable to use trichlorethylene in an anesthesia machine in which soda lime is present, even though the carbon dioxide absorber is shut off. Dr. Fabian has shown the longer the contact between trichlorethylene and the alkali, the greater the amount of toxic products formed. Perhaps the greatest hazard of trichlorethylene-alkali toxicity would occur when trichlorethylene inadvertently leaks into the soda lime and remains there for a period of time without the knowledge of the anesthetist. The toxicity will then appear in a later patient who will have had no trichlorethylene at all.

I have only one other comment with regard to the toxicity data in dogs. As I recall, most of the cases of human toxicity from industrial poisoning are manifest by trigeminal palsy, mental symptoms, and perhaps eye symptoms. I wondered how readily these would become apparent in animals.

Dr. Fred Woodson, Tulsa, Okla. It has been my clinical observation that Trilene left in an inhaler for one day or several days has lost its potency. In other words, it does not have the kick in it that it should, and I wonder if there were any decomposing elements, exposure to air or standing when it has not been bottled up which have any effect on its toxicity. I have not noticed any toxicity, but we use Trilene for short dental procedures and some of these are in offices which are not equipped with any absorbing or circle pull, merely straight, old fashioned exhaling technic in which the patient is not rebreathing, and it only lasts five minutes or ten minutes. But if Trilene is left in the container that evaporates it, it loses its potency and one needs a fresh supply on each use, if one uses it from day to day.

Dr. Harold F. Chase, Philadelphia, Pa. I want to ask Dr. Fabian two questions. In the original observations about Trilene, inhalation of minute quantities of it gave a rather prolonged relief of trigeminal neuralgia. Observation has been made in pathologic discussions that there had been shown to be actual changes in the nerves after inhalation of trichlorethylene. I wonder what evidence there is to that effect.

The other question: If one takes soda lime out of a cannister, particularly in some of our machines, there may be quite a lot of soda lime dust left in the cannister, and also, even though we shut off the cannister, there is still one part that is open and quantities of the ambient gases can back up in there. How much danger is there in refilling that cannister and going on with a closed system, from the effect of the dust reacting with the amount of trichlorethylene that has backed up in there? Should we bypass cannisters altogether when giving Trilene, or should we substitute a fresh, clean cannister after use of Trilene in a machine?

Dr. Fabian (Closing). In answer to the questions asked by Dr. Chase, I believe that by discarding the soda lime used in this particular circuit, one should have no difficulty in avoiding toxic responses to decomposed Trilene, since these products of decomposition are apparently bound chemically to previously used soda lime and are released only when such absorbent is re-used at a later time. All residual gases and vapors will be eliminated when one rinses the tubing and breathing bag between cases.

In answer to a previous question from the floor concerning the time of exposure necessary for production of toxic manifestations, it should be remembered that commercial and not medical trichlorethylene was being manufactured in those plants where workers had developed trigeminal pareses. In those cases several months or perhaps years of exposure to these vapors had occurred preceding the onset of organic lesions. Such exposure to toxic products of decomposition would not be met clinically unless related to the use of previously exposed soda lime and/or trichlorethylene which had been allowed to become unstable by prolonged exposure to heat and sunlight.

I wish to thank Dr. Keats for his excellent discussion of our paper.

CASE REPORT

Twenty-Eight Years of Suprapubic Drainage Following Injury to the Spinal Cord

MONTAGUE L. BOYD, M.D., *Atlanta, Ga.*

ONLY OCCASIONALLY does an advocate of suprapubic cystostomy for the treatment of disorders accompanying paralysis of bladder have the opportunity to report the late results of such management. The following case report is therefore of interest.

Case Report

In 1927 a girl of 17 had her twelfth thoracic vertebra crushed in an automobile accident. At laminectomy a transverse lesion of the spinal cord was found. Three days after the laminectomy I did a suprapubic cystostomy leaving a Pezzar catheter in the suprapubic opening.

Course. For 28 years she has had continuous drainage through the suprapubic tube. She has had the anticipated relaxation of the bladder neck, and therefore some urine leaks through the urethra. However, as long as continuous suprapubic drainage is effective the leakage is not annoying and this requires that the suprapubic tube must always be kept clean and free of urinary deposits.

She had developed an abscess in the gluteal region with sinus formation. At one time this was attacked surgically but some discharge from the sinus has continued.

Otherwise the patient has remained remarkably well. She spends her time in a wheel chair and takes care of the housework in her own room. More recently she has taken a part-time job.

She was admitted to the hospital in April, 1955, for a study of her condition. A cystogram was normal (Fig. 1). Plain films to include the genito-urinary tract revealed no stones in any portion. The tissues about the suprapubic tube seemed to be healthy.

The phenolsulphonphthalein test showed an output of 38.7 per cent in 30 minutes. The blood nonprotein nitrogen was 27.3 mg. per 100 cc. Red blood cell count was 4,200,000 and the hemoglobin 14 Gm.

Comment

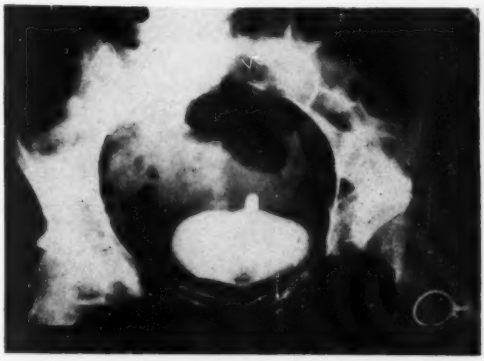
I do not believe that any other method of management of the urinary tract in a case such as this can so successfully prevent the formation of stones in the urinary tract. Furthermore, it seems to be the best method of avoiding injury to the bladder, urethra, and kidneys, as well as the general disturbances due to infection of the urinary tract.

Such management will be successful if attention is given to the following details: (1) frequent changes of the suprapubic tube; (2) attention to keeping the tissues clean about the tube; (3) the drinking of adequate quantities of water; (4) proper care of the bowels; and (5) the avoidance of foods and drugs which make the urine too alkaline.

With the application of a little care, leakage from the urethra in women can be avoided. In my experience, this is not true in women who wear urethral catheters, since the catheter tends to produce an increased relaxation of the urethra.

Catheters in men are equally unsatisfactory.

FIG. 1



Cystogram made with a Foley catheter in the urethra.

To those who are not looking for disturbances, they may seem to work well for a year or even a few years. However, the infection and irritation which the catheter either permits or causes in the urethra, by absorption, tends to impair the patient's general condition. This is seen time and again in patients who need bladder drainage in preparation for prostatectomy. I feel that patients having suprapubic drainage do better than with catheter drainage. Of course, with the Foley catheter, catheter drainage is so easy that nearly all of us now use this method and generally get into no difficulties. However, when drainage is necessary for many weeks I still advise suprapubic cystostomy.

Catheter drainage in the cases of paralysis is more injurious than in the non-paralytic. Under such circumstances the tissues are more readily injured by a foreign body and infection penetrates more readily to the deeper structures. (These factors are so well shown in the case in which bed sores develop unless the best care possible is used for the skin.) In the male, infections readily extend into the prostate and seminal vesicles, producing an injurious systemic effect even though the patient complains of no local symptoms. Many of them develop an epididymitis which cannot be overlooked as readily and frequently as seminal vesiculitis and prostatitis.

Summary

Only rarely has an observer the opportunity to follow the course of a patient having a suprapubic drainage of the bladder for 28 years. Such an instance has been reported. Proper care of the drainage tube and tissues surrounding it, as well as adequate intake of fluids, has prevented the complications of infection and calculus which might have been anticipated.

Fiftieth

Anniversary Meeting

Washington, D. C.

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Certain Problems of the Medical Management of Peptic Ulcer*

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The medical management of peptic ulcer has many facets. Improper attention to basic physiologic disturbances may well lead to failure in treatment.

Introduction

PEPTIC ULCER PHYSIOLOGICALLY REFLECTS the inability of localized areas of the stomach and duodenum to withstand the digestive action of acid gastric juice. In gastric ulcer, the output of hydrochloric acid is normal or low but its corrosive effect surpasses the diminished resistance of the gastric mucosa. In duodenal ulcer, the secretion of hydrochloric acid is very high and its digestive action exceeds the apparently normal duodenal mucosa. The hypersecretion in duodenal ulcer is demonstrable in studies of the fasting or basal secretion, following sham meals and after the administration of various gastric stimulants; it continues between meals, during the night and after the ulcer has healed. The role of hydrochloric acid is indicated further by the fact that peptic ulcer occurs only in those areas of the digestive tract exposed to acid and only among individuals capable of secreting hydrochloric acid. Free acid is demonstrable in all patients with benign gastric ulcer and with duodenal ulcer when adequate methods of analysis are employed. Both in gastric and duodenal ulcer, effective, continuous neutralization or complete elimination of the acid gastric content results in complete and sustained healing of the ulcer. Practically all technics for producing ulcers experimentally involve hypersecretion of hydrochloric acid or interference with the usual mechanisms for neutralizing and buffering the acid. The role of hydrochloric acid in the pathogenesis of peptic ulcer thus may be compared to that of the essential catalyst in a chemical reaction; other ingredients (etiologic factors) are involved in the process, but in the absence of the catalyst (HCl) the reaction cannot proceed.[1,2]

The mechanism of the hypersecretion in duodenal ulcer is not understood completely. Anatomically, the large outputs of acid seem to be correlated with an increased number of parietal cells in the fundus and body of the stomach. Histamine, acetylcholine and other chemical substances, such as serotonin, various hormonal factors, including gastrin from the antrum and adrenocortical hyperfunction via the hypothalamus and anterior pituitary gland, all have received consideration as possible causes of the hypersecretion. Present evidence tends to support the concept of vagal hyperactivity acting upon a more responsive gastric secretory apparatus as the most likely mechanism; however, other factors, chemical and humoral, undoubtedly are involved.

A priori, tissue vulnerability, localized or diffuse, would appear to be an important factor in the development of peptic ulcer. The nature of tissue resistance and the factors decreasing or increasing it are not known. Alterations in the rate of regeneration of epithelial cells, in the mucous barrier of the stomach and duodenum and in the vascular supply to the stomach and duodenum each may play an important role. For example, the thin, atrophic mucosa in gastric ulcer is more susceptible to hemorrhage and trauma and probably contributes to the lowered resistance of the stomach in gastric ulcer. Other, as yet unknown, factors also appear to be involved because chronic peptic ulcer does not occur in pernicious anemia with a severely atrophic mucosa, but without hydrochloric acid.[1]

Management of Peptic Ulcer

Tissue Resistance. In the absence of a known cause, the treatment of peptic ulcer

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continues to emphasize protection of the gastroduodenal mucosa from the digestive action of hydrochloric acid. This objective might be accomplished either by increasing tissue resistance or by permanently inhibiting the secretion of acid. There is no acceptable procedure for improving the tissue defenses directly. The value of tissue extracts, hormonal substances and other materials of uncertain composition and biologic action recommended for this purpose is not established. Tissue resistance probably is increased indirectly by improving the general health of the patient, avoidance of gastric irritants in food, drink and medication (alcohol, salicylates, phenylbutazone), and by decreasing or avoiding excessive physical and emotional fatigue.

Diet. There is no satisfactory evidence relating the development of the usual peptic ulcer in man to nutritional deficiency or to irritation of the gastroduodenal mucosa by food.[3] Nevertheless, diet is an important adjunct in therapy. Frequent feedings of soft, bland foods help to neutralize and buffer the acid gastric content; they also provide adequate amounts of calories and essential nutrients. The ulcer patient is capable of tolerating a more liberal diet than has been prescribed, and the extreme dietary restrictions of past decades no longer are recommended. On the other hand, a bland, nonirritating diet avoids gastroduodenal irritation and secondary rises in acidity; by buffering and neutralizing acid, the diet aids in the control of ulcer pain.

Antacids. Although food may lower gastric acidity, diet alone is inadequate for this purpose. Many antacids, singly and in combination, are available, including aluminum hydroxide and phosphate, magnesium trisilicate and hydroxide, tribasic calcium phosphate, and ion-exchange resins.[2,4] However, unless taken in very large quantities at hourly intervals, these preparations neutralize the acidity only partially, the pH of the gastric contents ranging between 2 and 3. Antacids are more effective in an intragastric drip, but this method is not practical for prolonged use. The occasional intake of antacids immediately after meals, a procedure apparently sanctioned by many physicians, does not neutralize gastric acidity adequately and reflects lack of knowledge of peptic ulcer and its treatment. Bismuth preparations, mucin and many proprietary products are worthless for the control of gastric acidity in man. Calcium carbonate is the most potent antacid in our experience; 2.0 or 4.0 Gm. hourly during the day and evening maintains the pH of the gastric contents between 4 to 5, and at this level practically all peptic activity is absent. Differences in the neutralizing efficiency of calcium carbonate probably are attributable to individual variations in the rate of gastric secretion and gastric emptying. Adequate control of gastric acidity is not accomplished readily in the patient with peptic ulcer even with calcium carbonate and requires continuous administration in adequate amounts. The *a priori* selection of antacids for clinical use, based upon laboratory tests, is unjustifiable, since the neutralizing efficiency of these compounds can be estimated with some accuracy only in patients secreting hydrochloric acid continuously.[4]

Constipation with fecal impaction may be a troublesome complication of antacid therapy, especially in older patients. This situation usually can be corrected by substitution of the more laxative magnesium carbonate for calcium carbonate, or by the combination of magnesium trisilicate with aluminum hydroxide. Daily rectal examinations may be necessary until the proper proportions of standard and laxative antacids are determined for the individual patient. In a few instances, the prolonged accumulation of hard fecal matter has produced stercoral ulceration of the bowel; fortunately, this occurrence is rare.

Therapy with milk and calcium carbonate also may be complicated by the hypercalcemic syndrome.[5] The characteristic symptoms include weakness, headache, malaise, distaste for milk, cream and food, nausea and vomiting. The important chemical features are: an elevation of the serum calcium to 15 and 18 mg. per 100 cc., no hypercalcuria, mild to moderate alkalosis, normal serum phosphorus, normal serum alkaline phosphatase, elevated blood urea nitrogen and temporarily depressed renal function. The syndrome has been observed more often in older men with hypertension and with pre-existing impairment of renal function. It occurs also in patients taking milk and cream and sodium bicarbonate, who have never received calcium carbonate. In one patient, the hypercalcemia was reproduced twice by the re-administration

of milk and calcium, but not when calcium carbonate alone was prescribed. In another patient with a bleeding duodenal ulcer, the hypercalcemia developing early in therapy subsided completely and promptly after the increased intake of fluids and electrolytes; and despite continued ingestion of calcium carbonate, the serum electrolytes remained normal. The clinical and chemical manifestations of the hypercalcemic syndrome subside promptly after discontinuance of the milk and alkali and the increased intake of isotonic saline, glucose and water. Calcium carbonate then may be resumed without further difficulty.

Antacid treatment, to maintain its usefulness, must be continued for long periods of time. The hourly program gradually is replaced by a two-hour schedule and later by antacids between meals and at night. Most patients avoiding recurrences of peptic ulcer usually continue diet and antacid therapy indefinitely. For convenience, calcium carbonate and magnesium carbonate, as well as other antacids, are available in tablet form; however, these preparations usually are less effective than powdered antacids. Many individuals find the prolonged intake of antacids tedious and distasteful. Therefore, inhibition of gastric secretion in peptic ulcer by antisecretory drugs, taken orally, would be of considerable therapeutic value. This intriguing possibility has stimulated interest in the synthesis of compounds inhibiting the output of hydrochloric acid, presumably by influencing the neurogenic and cellular phases of the gastric secretory mechanism.

Anticholinergic, Antisecretory Drugs. The principal therapeutic purpose of anticholinergic drugs in peptic ulcer is prolonged suppression of acid gastric secretion, permitting a more convenient program of fewer antacids and a more liberal diet. Numerous antisecretory compounds have been developed and studied in the past five years;[2,6,7] while many have been ineffective, several preparations definitely excel earlier antisecretory agents. Tincture of belladonna, in average doses, does not demonstrably lower the output of acid in peptic ulcer. Atropine sulphate may decrease the output of acid partially and temporarily in occasional patients, especially after parenteral administration; however, effective doses closely approximate toxic amounts. Synthetic atropine compounds also are ineffective for this purpose. The tetraethyl-ammonium compounds lower gastric secretion, but only when given intramuscularly in large amounts. The hexamethonium preparations may be more potent after oral administration but they cause distressing side effects, including postural hypotension and intestinal atony, and their antisecretory action is erratic.

The currently popular antisecretory drugs represent chemical combinations of the amino alcohol ester structure of synthetic atropine drugs with the quaternary ammonium configuration of TEA or hexamethonium. The first of these products, Banthine, may suppress hydrochloric acid completely for several hours when given intramuscularly in sufficient quantities. However, side effects develop in almost all cases. Banthine orally is considerably less potent; the volume of secretion may decrease but the concentration of acid is not reduced significantly, despite the administration of quantities causing pronounced side reactions. Prantal, 100 mg. four times daily, usually does not produce side effects but its antisecretory action is not impressive when measured in patients with duodenal ulcer. Larger amounts of these compounds undoubtedly would be more effective. Experimental compounds such as U-0229 are very potent antisecretory agents upon both intramuscular and oral administration in small (1 to 4 mg.) doses. However, they cause severe side effects of the type associated with an over-dosage of atropine. Compound U-0229, in total amounts of 6 to 8 mg. intravenously, suppressed the output of hydrochloric acid completely in patients with duodenal ulcer for periods up to 60 hours after discontinuance of the drug, a remarkable, if not practical, achievement.[8]

Pamine, (10 to 30 mg. daily), Pro-Banthine (60 to 120 mg.), Monodral (15 to 30 mg.), and Darstine (300 to 400 mg.) may lower gastric secretion effectively. Among other newer drugs, as Lusyn, Centrine, Pathilon, Malcotran, Marplan, Contral, Skopolate, Elorine Sulfate, Tricoloid, Piptal, Homatropine, Paragone, ML 412 (Maltbie) AP 396 (Abbott), the pharmacologic and clinical effects of these preparations are approximately similar. Some compounds may suppress acid secretion effectively with less frequent and more tolerable side effects than earlier antisecretory drugs

and for longer periods of time. Pamine, for example, has induced anacidity for periods up to eight hours after a single intramuscular dose of only 0.08 mg. As with all compounds of this type, much larger quantities are necessary for oral administration; presumably insoluble complexes are formed within the intestine, removing substantial proportions of the drug in the feces. The effective single oral dose of Pamine, depending upon the individual response, thus, may be 2.5, 5.0 or 10 mg.

The relatively large oral intakes of anticholinergic drugs usually are accompanied by side effects, especially dryness of the mouth, constipation, and, in males, by slowing of the urinary stream. Symptoms produced by some anticholinergic drugs, not by all, also include blurring of vision, headache, drowsiness, heartburn, cardiospasm, intestinal atony, tachycardia, mental confusion, visual and auditory hallucinations. These symptoms may be so troublesome as to necessitate discontinuance of the drug. In most cases, however, the side effects are not severe, decreasing or disappearing entirely during continued treatment. Currently available anticholinergic compounds should not be prescribed in the presence of pyloric obstruction because the inhibition of gastrointestinal motility intensifies the existing gastric retention; in patients with incipient glaucoma because of the possibility of increasing intra-ocular tension; in the presence of prostatic hypertrophy because anticholinergic drugs decrease the contractility of the urinary bladder and thereby increase the retention of urine; and in cardiospasm, because by depressing vagal function these compounds may intensify the physiologic difficulty.

The prolonged use of potent anticholinergic drugs may continuously lower the output of hydrochloric acid in some patients with duodenal ulcer; however, this effect is variable, unpredictable, or, when present, not necessarily sustained. Suppression of gastric secretion is more likely in the normal stomach or in patients with gastric ulcer in whom the output of hydrochloric acid is normal or low; however, in these cases also, the antisecretory effects are erratic. Furthermore, partial lowering of the acid output is not adequate for complete, sustained healing of gastric ulcer since total elimination of hydrochloric acid is desirable for this purpose. As with antacids, the antisecretory effect, when present, is limited to the period of administration. There is no significant or sustained after-effect; discontinuance of the drug is followed promptly by return of the hydrochloric acid to original levels. Antisecretory compounds are more likely to inhibit the fasting or basal gastric secretion than the tremendous outputs of acid produced under ordinary conditions in response to neurogenic, chemical, hormonal and other influences. Nevertheless, studies of basal secretion provide a useful and approximate index of the potential and relative antisecretory properties of these drugs. The gastric secretory response to sham feeding, presumably reflecting the cephalic phase of gastric secretion, also may be utilized for this purpose.

Anticholinergic drugs should be prescribed only as adjuncts to conventional treatment of rest, sedation, diet and antacids. Many clinical studies of antisecretory drugs in peptic ulcer are difficult to evaluate satisfactorily because of the subjective nature of the observations, lack of adequate controls and the relatively brief periods of observation. In general, anticholinergic drugs appear to have facilitated more effective relief of ulcer distress and to have decreased the incidence of complications. Present compounds are more potent and clinically more useful than belladonna, atropine and earlier anticholinergic preparations, since they effectively suppress acid production in some cases without significant side effects. On the other hand they have not provided the therapeutic solution hoped for originally. The ultimate objective of treatment with antisecretory drugs, the effective lowering of gastric secretion during oral administration for long periods of time, with little or no side effects and without toxic reactions, has not been attained, though some progress has been made. Continued research toward this goal by the organic chemist and pharmacologist, in cooperation with the clinical investigator, should continue, for the possibilities of this approach thus far have been investigated only partially.

Irritating Drugs. Several drugs prescribed frequently for arthritis and related disorders are irritating to the gastrointestinal mucosa and probably should be avoided by patients with peptic ulcer. Salicylates may injure the gastric mucosa, increase gastric acidity and

cause massive hemorrhage. The use of corticotropin, cortisone and other adrenal steroids also may be associated with the recurrence or new formation of peptic ulcer. The effect has been attributed to a rise in gastric acidity and in peptic activity secondary to adrenocortical stimulation via the hypothalamus and anterior pituitary gland.[9] A decrease in the quantity of gastric mucin during steroid therapy also has been reported in several cases.[10] However, the number of cases developing this complication is extremely small in relation to the enormous numbers of patients receiving these compounds. We have encountered peptic ulcer in only one of 180 patients with ulcerative colitis receiving large quantities of steroids for long periods of time; at least nine of the series with known peptic ulcer tolerated corticotherapy without symptoms.[11] Twenty-one instances of peptic ulcer were noted among more than 700 patients receiving ACTH and adrenal steroids at the University of Michigan.[12] Peptic ulcer did not develop in any of 109 patients with ulcerative colitis given ACTH or cortisone.[13] Though adrenocortical hyperactivity has been implicated in the pathogenesis of peptic ulcer, there is no acceptable evidence of adrenocortical hyperfunction in the usual peptic ulcer. The effects of corticotropin and adrenal steroids upon gastric secretion appear to require further study. We have noted a temporary increase in the output of hydrochloric acid in only one of 10 patients with ulcerative colitis receiving large quantities of steroids for periods up to 60 weeks; despite continued therapy, basal gastric secretion in this case returned to original levels.[14] The possibility exists that patients with duodenal ulcer may respond more readily than those with ulcerative colitis. Nevertheless, the tendency of the adrenal steroids to produce peptic ulcer appears to be limited to a very small group of peculiarly susceptible individuals. Phenylbutazone, another anti-arthritic drug, also may precipitate the recurrence or new development of peptic ulcer complicated by hemorrhage and perforation. Gastric acidity may increase temporarily, the rise occasionally approximating the response to the potent stimulant, histalog.[15] However, the action of phenylbutazone is not mediated via the adrenal cortex, as is shown by the fact that the increases in gastric acidity may occur in patients after bilateral adrenalectomy. Since similar increases may develop in patients with apparently complete vagotomy, the action of phenylbutazone does not appear dependent upon an intact vagal mechanism. The rise in gastric acidity may be related to irritation of the gastric mucosa locally. The concurrent administration of antacids in adequate amounts tends to protect the gastroduodenal mucosa from the irritating effects of salicylates and phenylbutazone and should be prescribed when the use of these compounds is contemplated.

Alcohol, Tobacco, Coffee. Alcohol stimulates gastric secretion, the increased output approximating the response to histamine; the effect has been attributed to release of histamine locally from the gastric mucosa and also to activation of the gastrin and vagal mechanisms. Alcohol also causes hyperemia and congestion of the gastroduodenal mucosa, presumably decreasing its resistance to exogenous and endogenous irritants. Alcohol, therefore, should be avoided by the patient with peptic ulcer. Coffee also stimulates gastric secretion, both in normal persons and in individuals with peptic ulcer. Caffein is a potent stimulant of gastric secretion and is used as a test of gastric secretory response. While small or moderate amounts of coffee are permissible, the excessive ingestion of coffee probably is harmful and should be avoided by the ulcer patient.

Several reports indicate that tobacco may stimulate gastric acidity in man.[16] However, the effects of tobacco upon gastric secretion and the gastroduodenal mucosa are not known precisely. Experimentally, tobacco did not appear to increase the ulcer-producing properties of histamine.[17] Clinical studies suggest that habitual smoking significantly reduces the beneficial response of ulcer patients to antacids.[18] Tobacco per se does not cause peptic ulcer and its use in small or perhaps moderate amounts may be permitted, if it promotes "relaxation." Excessive amounts of tobacco, however, are harmful and should be discontinued completely, especially in patients with a history of frequent recurrences.

In the absence of a specific and simple cure, the number of ulcer remedies remains enormous. Many have been thoroughly discredited. Current evidence indicates that the following substances also should be discarded for this purpose: detergents such as sodium alkyl sulfate, antihistaminics, bile salts, enterogas-

trone, histidine, pregnant mares' urine, sex hormones, posterior pituitary preparations, extracts of animal stomach, duodenum and colon, chlorophyll and cabbage juice.

Intractable or Refractory Peptic Ulcer. The term "intractable" ulcer implies a lesion not responding to treatment usually effective and, therefore, requiring operation. However, "intractability" is not always interpreted critically. Too often the label is applied casually and unjustifiably to ulcers which have failed to heal during careless or inadequate medical treatment. The program prescribed in an individual case may be inadequate or the patient may not adhere to the regimen, the patient-physician relationship may be inadequate, or the emotional difficulties of the patient may be pronounced. The ulcers actually are not refractory, for, under proper circumstances, they heal promptly and completely. In the truly intractable peptic ulcer treatment ordinarily effective fails to promote healing or to prevent complications. The underlying cause may be serious emotional difficulties, uncontrollable gastric hypersecretion, decreased tissue resistance, or irreversible complications, such as obstruction. Evaluation of an "intractable" or "refractory" peptic ulcer requires careful study of all possible etiologic and contributory factors. Occasionally, thorough review of a problem case may reveal factors of decisive importance, correction of which may be more effective than conventional medical or surgical treatment. Illustrative cases follow:

A. V. (Unit No. 403855), a man of 49 gave a long history of peptic ulcer, beginning in 1926 with perforation treated by surgical closure. Subsequent recurrences were managed by gastroenterostomy in 1928, vagotomy in 1947 and by gastric irradiation. Between 1930 and 1950 there was continued marital discord and frequent recurrence of the ulcer. Since the patient divorced his first wife and remarried happily in 1950, he has remained in excellent health with minimal medical treatment.

G. M. (Unit No. 520759), a man of 56, had a duodenal ulcer in 1944 which eventually responded to careful antacid treatment after casual therapy had failed. A recurrence in 1950 again failed to respond to occasional antacids, prescribed elsewhere. Opiates relieved the ulcer pain only partially and operation was advised. Careful study demonstrated an uncomplicated duodenal ulcer and gastric hypersecretion. Calcium carbonate, 2.0 Gm. hourly, did not neutralize the acidity adequately or relieve the ulcer distress; 4.0 Gm. doses given hourly day and night were more effective, relieving the pain, permitting complete healing, and obviating the need for operation. The patient remains well.

In E. M. (Unit No. 460965), careful antacid therapy, supplemented by gastric irradiation, failed to eliminate the hydrochloric acid completely and a benign gastric ulcer recurred; gastric resection was successful and the patient is free of distress.

R. H. (Unit No. 458627), a man of 52, had frequent recurrences of a duodenal ulcer since 1934, which responded poorly to indifferent and inadequate management prescribed by physicians or self-imposed by the patient. The recurrences ultimately healed. He entered Billings Hospital for the first time in 1949, because of hemorrhage and gastric retention; vomiting and gastric aspiration resulted in an hypochloremic alkalosis, responding to the administration of electrolytes and water. During the same hospitalization, the duodenal ulcer perforated, required operative closure, and then vagotomy and gastroenterostomy. The patient remained well for four years, finally succumbing to severe hypertension and cerebral hemorrhage.

Perhaps the most refractory peptic ulcer in our experience is shown in the following case:

G. J. (Unit No. 130625), a man of 52 years, had a sequence of events as follows:

1928		Onset of duodenal ulcer
1930		Hemorrhage; gastroenterostomy
1934		Jejunal ulcer
1935	(March)	Jejuno-colic fistula Normal gastrointestinal series; continuity restored
	(September)	Recurrent duodenal ulcer
1936	(April)	Partial gastric resection
	(September)	Ulcerative jejunitis, jejunal ulcer
1937	(February)	Jejunal ulcer with hemorrhage
	(June)	Gastric irradiation, acid decreased—ulcer healed
1939		Acid returned, jejunal ulcer responding to antacid therapy
1941	(April)	Jejunal ulcer Second course of gastric irradiation, acid decreased, medical treatment effective
1948		Fatal hemorrhage Autopsy: multiple gastric ulcers.

The inexorable tendency to the recurrence of peptic ulcer illustrated so dramatically in this case remains unexplained; however, the sequence of events appears to indicate the important role of hydrochloric acid. The most comfortable period for the patient, 1941 to 1948, followed a second course of gastric irradiation causing prolonged, significant lowering of acid secretion. The recurrences of peptic ulcer and the fatal hemorrhage each were preceded by return of the acid to original excessive levels.

Comment. The factors responsible for intractability and the poor response to therapy in some patients, in contrast to the usual satis-

factory results, are as obscure as the cause of peptic ulcer.

Gastric Irradiation. Mild roentgen irradiation of the fundus and body of the stomach also has been utilized to decrease or completely eliminate the secretion of hydrochloric acid and thereby to reduce the frequency and severity of ulcer recurrences.[2] Approximately 1,400 patients have been treated with gastric irradiation since May 1937, without demonstrable harmful effects and, in many instances, with highly beneficial results. Approximately 1,600 roentgen units, total depth dose, now are administered in 10 divided daily doses over fluoroscopically-outlined anterior and posterior portals. Histologic studies indicate that the radiation causes necrosis of the chief and parietal cells, resulting occasionally in complete loss of the glandular substance. The changes are temporary, and in most cases the gastric mucosa apparently returns to normal. The degree of reduction in acid secretion following irradiation and the duration of this effect vary. The output of hydrochloric acid diminishes in the vast majority of cases, at least temporarily. This effect may continue for months and years. The total elimination or significant lowering of hydrochloric acid results in complete and sustained healing of the ulcer. Recurrence of the lesion invariably is preceded by the reappearance of acid. The continued favorable course of peptic ulcer in many patients with apparent return of acid secretion to previous levels, as indicated by tests with histamine or histalog, may be related to a change in the continuous output of acid characterizing doudenal ulcer to the intermittent secretion of the normal stomach. Irradiation in the absence of a significant lowering of gastric acidity does not influence favorably the usual course of peptic ulcer. Though gastric irradiation is not a cure for peptic ulcer, the procedure may be a useful adjunct to conventional treatment, decreasing the frequency and severity of recurrences and the incidence of complications.

Gastric Retention. Gastric retention in most patients with peptic ulcer is caused by inflammation and edema around an active ulcer, temporarily narrowing the channel through the pylorus and duodenum. This complication usually responds to a medical regimen of nothing by mouth, continuous gastric aspiration and the parenteral administration of adequate quantities of electrolytes and fluids. The continuous withdrawal of hydrochloric acid removes the most important factor in the continued activity of the lesion, permitting the ulcer to heal; the edema and inflammation subside and the channel once more is patent, as indicated by decreasing volumes of gastric aspirate. In perhaps 15 per cent of cases with gastric retention, the obstruction is caused by scarring and cicatricial narrowing of the pylorus and duodenum. Medical management is inadequate under these circumstances and gastric aspirates remain excessive. This type of obstruction requires surgical treatment, either gastroenterostomy and vagotomy or gastric resection. Nightly gastric aspiration, in addition to its usefulness in evaluation of the problem of retention, also is helpful in relieving severe ulcer pain. Pronounced depletion of electrolytes and fluid may occur in patients with gastric retention, as a result of vomiting or aspiration. This complication is characterized chemically by an hypochloremic, hyponatremic alkalosis; since the potassium content of gastric juice is four or five times larger than the blood potassium, loss of this ion also may be considerable.[19] Treatment consists in recognition of the possibility of hypochloremia and alkalosis in patients with gastric retention, frequent measurement of the serum electrolytes, the administration of appropriate amounts of sodium, potassium, chloride, glucose, and water, and discontinuance of aspiration as soon as practical.

Hemorrhage. The treatment of massive hemorrhage from peptic ulcer is essentially a medical problem, except in severe persistent bleeding.[20] Therapy includes sedation, frequent measurements of the blood pressure and pulse, and continuous neutralization of the gastric contents during the day and night. Glucose in water or isotonic saline may be administered subcutaneously to prevent dehydration and to maintain an adequate flow of urine; large amounts of fluid intravenously have been associated with continued or intensified bleeding and, therefore, are not prescribed. Blood transfusions are given in quantities of 500 cc., as needed to maintain an adequate blood volume. There is little danger of renewed or intensified bleeding following blood transfusions, in our experience. Inability to maintain an adequate blood volume after the administration of 1,500 to 2,000 cc. of

blood during a day or any part of the day indicates severe bleeding, presumably from a large artery, requiring prompt surgical attention. In patients responding to medical management, additional soft, bland foods are permitted three to six times daily; this schedule subsequently is expanded to a three meal ulcer diet. The advantage of feeding over starvation in bleeding peptic ulcer is reflected in the contrasting mortality figures,—3.5 per cent for the program of feeding compared with 13.7 per cent for the regimen of starvation. On the other hand, avoidance of food for very brief periods may be desirable in selected cases. In the presence of vomiting, food and liquids by mouth are withheld temporarily and fluids are given parenterally. In some patients with bleeding duodenal ulcer, gastric aspiration, by removing the hydrochloric acid, facilitates healing and the cessation of hemorrhage, obviating the need for operation. Gastric lavage with ice water or with various hemostatic medications has not been necessary in our experience. Anticholinergic or gastric antisecretory drugs may be prescribed to inhibit the secretion of acid; gastric retention and constipation develop occasionally during such therapy, necessitating discontinuance of the medication, at least temporarily. Increased cooperation between the internist and the surgeon has improved the care of the patient with bleeding peptic ulcer and has clarified the indications for operation. Bleeding is more severe and more likely to persist in patients 45 or 50 years of age and older than in younger persons; operation, therefore, is indicated in "older" patients not responding promptly to medical treatment. Since the hazards of surgery likewise are increased in this age range, the surgeon also must accept a higher calculated risk. Operation is indicated in bleeding peptic ulcer under the following conditions: (1) severe, persistent hemorrhage during medical treatment; (2) recurrent bleeding; (3) stomal ulcer with hemorrhage; (4) hemorrhage and perforation; and (5) hemorrhage and pyloric obstruction or midgastric narrowing. The decision for operation usually is made during the first 48 or 72 hours, because complications and mortality rate rise with persistent uncontrolled hemorrhage. Occasionally, the decision may be deferred for several additional days, provided the patient's general condition remains good and the blood volume remains adequate. The operation of choice in massive hemorrhage from peptic ulcer is partial gastric resection, excision of the lesion if possible and ligation of the bleeding vessel. Gastroenterostomy alone or with vagotomy is not a satisfactory operation for acute massive hemorrhage. "Blind" gastric resection has been performed to control bleeding from tiny gastric erosions, so small as to escape recognition clinically or at operation. The results in some cases have been excellent, though opinions vary as to the routine applicability of the procedure. Surgery does not protect completely against recurrent hemorrhage, although the possibility is greatly reduced. The postoperative problems of dumping and nutritional depletion may be very troublesome. The risks of gastric surgery, especially for massive hemorrhage, are not insignificant. Death from massive hemorrhage usually is attributable to uncontrolled bleeding (medical or surgical), pulmonary complications, especially aspiration pneumonitis, renal failure, operative error and peritonitis. Further decreases in the mortality rate will depend upon the avoidance of these complications, the maintenance of normal blood volume, electrolyte and fluid balances, and perhaps upon prompt surgical treatment in those older patients not responding to *careful* medical therapy.

Recurrences, Emotional Problems. Recurrences of peptic ulcer are common with any type of therapy, medical or surgical, that does not permanently decrease or abolish completely the production of hydrochloric acid. The conditions or circumstances usually associated with recurrences include physical fatigue, sustained emotional tension, excessive use of tobacco, alcohol and irritating drugs, dietary indiscretions, inadequate treatment of the original ulcer, and intercurrent illness such as respiratory infections. These factors, of course, are among the usual stresses of life, associated with the recurrence of other chronic illness. Hence, their effects probably are nonspecific, although no less disturbing. The tendency to recurrences may be decreased and their severity diminished by a program emphasizing complete healing of the active ulcer, careful supervision of the patient subsequently and control of those factors associated with recurrences, namely, sufficient rest and recreation, a "life of moderation" and identification and control of nervous factors are important considerations. Management of

the emotional problem often is difficult and may be impossible. A useful approach, in some patients at least, consists in identifying the difficulty (domestic, occupational, social, environmental), attempt at solution by avoidance, re-orientation of the patient and by release of tension in adequate rest, regular habits of living and in pleasant recreational activities. Mild sedatives, such as barbiturates and the newer "tranquilizers," are helpful in promoting rest and relaxation. The sympathetic, interested, yet objective support of the attending physician can be very effective in dealing with this phase of the ulcer problem. Formal psychotherapy is rarely necessary, and the role of the psychiatrist in peptic ulcer, except in a very small proportion of cases, is negligible.

Conclusion

Despite the difficulties and inadequacies of medical management, current methods of treatment, when utilized properly and continuously, are highly effective in the vast majority of patients with uncomplicated peptic ulcer. The fact that these measures are, in a sense, nonspecific, does not justify their casual and indifferent application. Further progress in therapy will depend upon increased knowledge of the pathogenesis of peptic ulcer, especially the nature of tissue resistance and the mechanism of secretion of hydrochloric acid, and perhaps upon the development of an effective medical technic for producing sustained gastric anacidity. These objectives at present may seem unattainable, but in relation to the remarkable advances in medicine achieved in our lifetime they should not be regarded as impossible.

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—W. Raymond McKenzie, M.D., *Baltimore, Maryland*

Radiation Protection for the General Practitioner*

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The increasingly widespread use of the x-ray in office practice raises very practical problems in safety involving physicians, their helpers, the patient and the neighbors. The average doctor does not have the knowledge to protect himself and others against the hazards of excessive irradiation. He should get expert help in these matters.

The Problem

IN THIS PAPER AN ENDEAVOR WILL BE MADE to direct attention to some of the more important aspects of radiation protection and shielding, particularly as they may apply to the problems of the general practitioner in his use of x-rays for diagnostic purposes. Since x-rays are not used extensively by the general practitioner for direct therapeutic purposes, problems in this area may be neglected for purposes of the present discussion. An important exception may be in the case of x-rays as a dermatologic therapeutic agent, but such use is largely limited to the specialist.

No attempt will be made to offer specific solutions to the general practitioner's problems of protection. The problems are well understood and the means for their solution are readily at hand. Basically the problems of protection for the general practitioner are no different from those of the radiologist, and for practical purposes their solution may be found in the recommendations of the National Committee on Radiation Protection, specifically in National Bureau of Standards Handbooks 59 and 60 prepared by that committee.[1-3]

If one accepts the statement that the problems of the general practitioner and radiologist are basically similar, it is logical to ask why the general practitioner should be singled out for special consideration. There are a number of important reasons.

First, there are more x-ray units in the hands of the practicing physician than the radiologist, by a factor of about 10 as shown in table 1.

From the point of view of the sheer number of users the magnitude of the problem puts the general practitioner in a special position. This may be offset somewhat by the fact that the use factor per individual is probably much lower, i.e., the actual quantity of x-rays generated per day is less.

Secondly, the use of diagnostic x-rays by the general practitioner is usually in the role of a secondary tool in comparison with all of the other tools and technics that he must master. Hence it is only relatively rarely that the general practitioner has acquired the highly specialized background in radiologic physics necessary to fully appreciate and understand the technical aspects of radiation protection.[4]

Thirdly, x-ray equipment in the hands of the general practitioner is much more frequently used in physical locations, such as in homes or apartments, not specifically designed or planned for such use. Offices of the general practitioner are much more likely to be located in homes, commercial office buildings, or apartments than are the offices of radiologists.

Fourth, because x-ray diagnosis is a secondary tool it is also a secondary, even if appreciable, source of income. Hence, the x-ray

TABLE 1

USE OF X-RAY EQUIPMENT IN THE U. S.[4]

	Number	*Per Cent*
Dentists	65,000	51.6
Practicing physicians	32,000	25.4
(General practitioners)	(20,000)	(15.9)
Hospital and clinic	15,000	11.9
Chiropractors	7,300	5.8
Osteopaths	3,800	3.0
Radiologists	3,000	2.4

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equipment of the general practitioner may be expected to be less expensive, less well shielded and used longer into obsolescence than comparable equipment used as a major source of income. Similarly, it is not unreasonable to expect more "cutting of corners" in the shielding of the rooms and operators. Based on the lower work load this may be justified, but the proper shielding can only be assured by careful analysis and not by guess work.

There is an additional problem of concern to *all* users of radiation. Unless radiation is used wisely and safely an increasing pressure to control and regulate its use by state agencies may be expected.[5,6] For the reasons enumerated above, failure of the general practitioner to recognize his radiation safety responsibilities may be instrumental in hastening such regulation and possible restriction.

In matters of shielding and protection there are four major groups of persons that must be considered: (1) the physician himself, (2) the nurse, technician and office staff, (3) the patient, and (4) the neighbors, or persons outside the confines of the office. The first three groups are subject to the complete control of the physician. He cannot only measure and control the radiation atmosphere within which they work, but he can control their exposure habits, and examine them for any possible deleterious radiation effects. The last group is essentially beyond his control and so for their safety he must be doubly cautious.

Permissible Exposures to Radiation[7, 8]

The basic maximum permissible exposure of the whole body to radiation is 0.3 roentgens per week as measured in air. From this are derived other weekly permissible exposures under special conditions, such as 300 milli rads for the gonads, 450 mrad for the skin and lens of the eye, 1,500 mrad for the hands and feet and so on. It should be emphasized that these allowances are *maximum* values, and that radiation exposure should be kept as low as possible. Further, they are for occupational exposure under conditions where presumably some degree of watchfulness can be exercised over the persons so exposed in the course of their work. Exposures within the above limits may be incurred for the duration of one's adult lifetime without serious expectancy of any detectable injury to that person. Genetic damage is considered only secondarily in arriving at these limits.

The problem with respect to nonoccupational exposure is somewhat different. A question of ethics arises when one allows radiation to escape its place of use and expose persons to its effects under conditions that are utterly and totally beyond their knowledge and control. Such promiscuous exposure of persons including women and children can also influence our genetic picture if the number were allowed to become large. Primarily for the latter reason, the nonoccupational exposure limits for x-rays are 1/10 of those for radiation workers, except that they may be computed or averaged over a year instead of a week.[9]

If the whole population were to be exposed to radiation the average exposure per individual per reproductive lifetime should not exceed some low value, of the order of 20 roentgens.[10] Since this is averaged over the whole population some persons may accept more because others will have received less. But with the increasing use of radiation, and the very low lifetime exposures allowed, it behooves us to make every effort to eliminate unnecessary radiation exposure.

Since such nonoccupational exposures are based in the main on genetic considerations, the radiation that concerns us most in matters of protection, is that which reaches the gonads. In the diagnostic range of energies this may at times influence the protection requirements differently for men as compared with women. For very soft radiation the ovaries receive substantial protection from the surrounding body tissue whereas the testes receive virtually none.

Exposure and Protection of the Patients

The patient is, of course, the principal recipient of a radiation dose, but the fact that he is under diagnosis is no excuse for his exposure to more than the minimum quantity of radiation compatible with the diagnostic results sought.

Too often the exposure of the patient is increased unnecessarily with little thought beyond the immediate situation at hand. One

must give thought to an individual's lifetime exposure of the gonads; when it is realized that this may be as low as 20 roentgens (on the average) it is clear that one cannot play loosely with radiation exposure.

As an indication of the magnitudes of exposures under normal conditions a few are listed in table 2.[11]

The figures in table 2 are based on examinations made by radiologists and are not necessarily the same as are to be expected for the general practitioner. No comparable data from the general practitioner are known. It is probable that the ratio of general radiographic and fluoroscopic work by the general practitioner will show a larger fraction of fluoroscopy. It is also probable, for reasons to be discussed below, that the average dose per examination will be higher for the general practitioner.

It will be noted that the entire dose of the examination does not necessarily reach the gonads,[12] and the exact percentages are necessarily very difficult to state.[13] The percentages of the dose reaching the gonads should not be considered as quantitative, but more as illustrative. Their exact determinations are very difficult and will vary considerably from person to person. The doses in column two and described as "average" have little significance as such—one simply cannot average doses except under very limited circumstances.

However, it must also be noted that the fluoroscopic examination, which gives the highest body dose, may also be expected to give the highest gonad dose. The magnitudes of the gonad dose per examination are such as to dictate the utmost caution in the use of fluoroscopy. The gonad dose from radiographic examination, other than in the pelvic region, can usually be neglected in comparison.

TABLE 2

AVERAGE RADIATION EXPOSURES

	Average Dose	*Gonad Dose*	*Per Cent of Examinations*
General radiographic	2.7 r	0.1—10%	52
Fluoroscopic (G.I.)	65 r	20—50%	15
Photo fluorographic (chest)	1 r	1%	33
Extremities, radiographic	2 r	0.1%	10
Chest	0.1 r	1%	37
G. I. series	33 r	25—50%	18
Pregnancy	20 r	10—30%	1

Exposure of the General Practitioner

The examining physician may receive exposure from several principal sources such as:

1. Scattered radiation from patient,
2. Scattered radiation from improper cones and through the Bucky slot,
3. Direct radiation around screen edges,
4. Scattered radiation from walls and floors, and
5. Direct and scattered radiation on hands.

As a very rough rule it can be said that the level of scattered radiation at a point 1 meter from a scattering surface will be 0.1 per cent of level of the radiation incident at that surface. The handbooks of the National Committee on Radiation Protection recommend the use of this figure for computing protection requirements.[2]

Let us then consider the dose to be expected by the physician in the course of a fluoroscopic examination. For a patient dose of 60 roentgens the unprotected physician at one meter would receive .06 roentgens or 60 milliroentgens (or about the permissible daily dose). But in general he is not more than 0.5 meter away so that his dose will be 4 times larger, or 240 milliroentgens. A large fraction of this may be expected to reach his gonads. Of course the case outlined does not take into consideration the wearing of a protective apron, but this is often omitted.[14-16] There is also the possibility of his receiving scattered radiation from the walls and floor against which the apron would offer only partial protection.[17] His exact dose is difficult to determine, but it is easily possible for him to get his full day's permissible exposure from just one prolonged gastrointestinal examination.

In the case of horizontal fluoroscopy, an additional hazard may arise from radiation leaking through the tube housing or escaping from the cone and falling directly on the trunk region of the physician. This would be added to the scattered radiation from the patient. It can also be shielded off rather easily by suitably designed closures over the Bucky slots, built-in metal aprons or other means. But these are apt to be the very items omitted from the older, the less expensive, or less critically designed apparatus.

In the best designed equipment the screen moves with the tube and the diaphragms are so set as to never permit the escape of the direct beam beyond the edges of the protection glass on the screen. Again, with older apparatus, or equipment on which protection is minimal, this feature may be lacking, and the general practitioner gets the dose.

Exposure of the Office Staff

The general practitioner will only rarely have a trained x-ray technician available in his office. This will have certain consequences. If assisted by his office nurse, he will be assisted by a person generally untrained in the many little facets of protection that make for personal safety. He must therefore be prepared to provide the training; he must, himself, be sufficiently cognizant of the problems to adequately train his staff. For example, he should realize that a nurse standing a yard away from the patient during a fluoroscopic examination may be expected to receive 1 per cent of the patient dose (i.e., 60 milliroentgens for a single gastrointestinal examination).

For lack of a technician the general practitioner will do most of his own exposures, film working, positioning, etc. He will therefore himself receive the dose that in a full-time x-ray office will be distributed between the doctor and the technicians. Because his daily work load is not as large as in the full-time office, his exposure will be less, but he should think about it and maybe do something about it.

Exposure of his staff or patients in the waiting room is more likely in the office of the general practitioner than in others for two main reasons. As already noted his office will generally not be designed for shielding against radiation. In addition, x-ray equipment is often added to an existing office suite where little attention can be paid to its location with respect to office workers; it has to fit in where it can.

Exposure to Neighbors

As already noted, the permissible exposure for persons not employed in the medical establishment is only one-tenth that for employees, except that such exposure may be averaged over 12 months.

Great care should be given to this particular problem both from the ethical and legal viewpoint. In determining radiation dose outside the installation, whether by actual measurement or by computation, one should use safety factors freely. Work loads should be figured carefully and then multiplied by 2 to 5 to allow for growth. The beam should always be assumed to be pointing in the most disadvantageous direction. The occupancy of the outside space should be estimated on the high side. For example, an apartment should be considered as occupied 100 per cent of the time even though you happen to know that the present occupants both work away during the day.

Protection in the form of walls, barriers or other means are always more economically installed in advance than after an installation is completed and in operation. In many instances ordinary building materials will provide the needed protection at no extra cost, but this must be determined by calculation or measurement, and not by guesswork. Protection for a large work load and 100 per cent occupancy or adjacent rooms will usually not be prohibitively expensive; short-cuts are unwise and may be costly.

Influence of Technics on Radiation Exposure

The particular technics used by the general practitioner in x-ray examinations may have a substantial influence upon his problems of protection. It is in this regard that his situation may differ most markedly from those in the specialized x-ray clinic. Attention will be directed to some of the differences in order that the general practitioner become aware of them and, when indicated, do something to reduce the concurrent hazard.

As already noted the highest doses are received by patient and physician during fluoroscopy. This applies even when maximum efforts are made to reduce the dose rate and time of exposure. Practices of the office physician generally tend to increase both. His general procedure is to interview and examine a patient in such a manner that the x-ray examination is only one of the facets. He is thus changing back and forth from routine clinical to x-ray examination, and in the course of a day from patient to patient.

In order to take full advantage of the shadows of fluoroscopy, acute vision is neces-

sary. This can only be acquired by working in a darkened room and with eyes suitably adapted to the dark. To acquire suitable dark-adaptation it is necessary that he remain in a darkened room or wear darkened goggles for periods ranging from 20 to 30 minutes. Dark adaptation of only 3 to 5 minutes is a great help in reducing exposure; in fact, any dark adaptation is better than none at all. But in a busy office it is often considered impractical for the physician to do even this. To overcome this handicap, the most common procedure is to turn up the tube current in order to produce a brighter image on the screen. There may also be the tendency to prolong the examination in an endeavor to see the most under poor operative conditions. Each of these actions results in greater dosage to the patient, and more stray radiation to himself and others around him. Both are difficult to avoid under conditions commonly found in the office of the general practitioner, unless he is able to schedule a number of x-ray examinations to follow quickly, one after the other.

A related difficulty arises in connection with radiography, although the consequences are not as serious. A key to radiographic success is the degree of testing and control of the processing solutions and technics. Where films are processed in the small office, both solution and technics are likely to be far from ideal. To overcome this there is a tendency to overexpose the film and then only develop it up to the point where the desired contrast is believed to have been obtained. Since wet- and dry-film contrast can be deceptively different, "retakes" are often called for. Regardless of the ultimate film quality, this procedure of overexposing the film increases the dose of radiation to the patient, physician and others. Of course, a "retake" doubles the exposure for all.

Another variable source of stray radiation is related to the size of the fluoroscopic field used. The smaller the volume of the patient that is irradiated, the less will be the scattered radiation from the patient. Since the irradiated volume is controlled by the size of the field, it is important to have a variable field, commensurate with the desired diagnosis sought. It is only rarely, and for a short time, that a full field is necessary.

As a result of his studies Sonnenblick has listed a number of recommendations for use in connection with fluoroscopy;[18] some have been discussed above. His recommendations are as follows:

1. Exposure at table top not to exceed 20 r per minute; output determinations should be made at repeated intervals; awareness of change as x-ray tube ages.

2. Added filter of 2 mm. aluminum.

3. Target-table distance of at least 12 inches, preferably more.

4. Use protective equipment such as lead-rubber gloves and aprons, lead-backed chairs, palpation spoons; this equipment to be checked occasionally for possible leakage through displaced lead.

5. Awareness of scatter radiation from patient, screen, walls, and floor; potential large cumulative dose received from unit located in a narrow corridor or room; film badges from a concern such as Tracerlab may be used to measure direct and scatter radiation received.

6. A 1 to 2 inch unilluminated border on the screen; the entire screen ought not be illuminated.

7. Suggestions for correct usage include: (a) accommodation of vision with tinted glasses (red); (b) small fields on screen; (c) examinations conducted as rapidly as warranted; (d) milliamperage held as low as possible and not to exceed 5; (e) dial settings could be varied for patients of different body thickness.

8. A self-limiting fluoroscopic timer (a thought for the manufacturer).

9. No indiscriminate exposure, particularly of infants and children; if feasible, election of films rather than the fluoroscope.

A last source of radiation exposure is dependent upon the versatility of the equipment available to the general practitioner. He can, of course, have a single piece of equipment that embodies most (though rarely all) of the features necessary for all types of radiographic and fluoroscopic examinations. At best it will be very costly and hence difficult to support. He can, with ingenuity, overcome most of the shortcomings, but a considerable number of his alternate technics will result in more radiation exposure to his patient and

himself; it is doubted whether any will result in less exposure.

The practicing physician may well inquire as to sources of guidance in matters of radiation protection. Unfortunately, there is not a large number of persons qualified to provide such guidance and the geographical distribution of these few is not good. Some general references on the subject are given at the end.

If in the meantime the physician wishes to make some rough checks for himself, he may use the time-honored dental film method. A paper clip is clipped over a dental film and *taped in place so that it cannot shift.* The film is then worn at the waist by the physician or nurse for a period of two weeks. If upon processing, there is only a very faint image of the clip, it is probable that the working conditions are safe. On the other hand, if the image is pronounced, i.e., there is considerable darkening of the film, further investigation is indicated. Commercial film-badge service can be bought for a very nominal sum.

To check the areas outside the office that may be occupied by persons not working with radiation, the film should be exposed for 20 weeks (the permissible exposure for such persons is one-tenth that for occupational exposure). In this case the dental film should be additionally wrapped in black photographic film paper, since the average dental film packet is not completely light-tight. In estimating the probable exposure of persons in such outside areas, the occupancy factor should be taken into consideration.

Summary

In summary, it would appear that from every aspect, the disadvantage under which the average general practitioner has to use x-rays as a diagnostic tool, leads him to accept more rather than less radiation exposure per examination as compared with that in a specialized x-ray clinic. He is saved from more serious consequences mainly because his daily work load is less. Nevertheless, on the sound philosophy that no unnecessary radiation is good for anyone, he should make every effort to reduce radiation exposure to his patients, his neighbors and himself to the absolute minimum. His failure to accept the challenge will provide useful ammunition to those who want to control his use of radiation anyway.

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Discussion (Abstract)

Dr. Vincent P. Collins, Houston, Tex. There are approximately 40 times as many nonradiologists using x-ray equipment as there are radiologists. A widely accepted set of figures indicates that radiologists have eight times as much leukemia as the rest of the population. If that is so, the 40 times as many nonradiologists who are subject to an equal exposure should either have shown or should be going to show an interesting series of obituaries in the *J.A.M.A.*

Dr. Taylor. Dr. Collins, I do not know how thorough the studies have been in the way of including nonradiologists who have been using x-rays in their offices. I think if we accept this comparison, we would have to say that this probably means that the use factor of the general practitioner is at least eight times less than for radiologists.

This saves the general practitioner, in fact, the

general practitioner is saved by a lot of things. He will not, or rather, his future generations following him will not in all likelihood show up with genetic damage to the same extent, perhaps, as the radiologist because he starts his use of x-rays later in life. He has done most of his creating by the time he has gotten any appreciable dose of radiation. The radiologist starts his x-ray work as soon as he gets out of medical school, or as soon as he gets through his internship, and he may get large exposures before he is through producing his family.

This question of genetic damage is one that is of increasing concern to all of us. I do not want to overemphasize it, as it has been in some cases, but I do not want to minimize it. When we are talking about the genetic damage to patients, it is one of the limiting factors that is going to enter very strongly, as it has already entered to some extent, into our setting of permissible exposures. There are some indications that permissible exposures may be lowered in the future because of our increased knowledge of genetic damage. As you know, they have already been lowered by a factor of two as of about five years ago. They may have to be lowered again.

Dr. J. M. Dougall, Houston, Tex. I was very much interested in listening to this paper. Two points came to my mind. This, I do not think is of critical importance to us as radiologists because we try to consider all of these factors in our practice. However, I believe it is very important to others because very rarely does one of our general surgeon or general practitioner friends buy an x-ray machine without coming and saying, what shall I buy and how shall I put it in?

This problem is very well presented at this meeting. The one factor that comes to mind is to have us all remember to warn our friends who come and ask what to buy and when to buy it, that they should have a little bit of knowledge of the exposure of their personnel. One thing I have always found is that the nurse, usually not a technician, who operates the machine most of the time, will always stand at the side of the patient wherever the patient might be. One thing I am always sure to do is to warn the doctor that whenever he is operating the machine his personnel should stand behind him.

The other factor which is often missed, is that we forget to tell our friend to be sure he has an aluminum filter in the housing underneath the table. So often tubes are used without aluminum filters.

Dr. Taylor. The point with regard to offering advice to prospective purchasers is an excellent one, where these purchasers will seek advice. There is no way to make them seek advice unless somehow or other they are made more conscious of their responsibilities and of the problems that are involved.

I do not know, and I have not inquired, as to whether or not anything is taught about radiation safety in medical school, even for two hours of the entire course of teaching. I suspect that even two hours teaching of radiation protection in medical school would possibly leave some impression on the young physician to the point where he at least will seek advice when he considers putting in x-ray equipment at some later time.

The question of filtration is an important one. The newest recommendations coming out by the National Committee on Radiation Protection will call for a minimum of 2.5 mm. equivalent of aluminum filtration in the beam. This is in the way of providing the sort of protection that was suggested.

There are also factors that enter the problem involving the distance between the tube and the patient during examination. I had better not try to quote these numbers, but there are optimum distances that provide the maximum safety to the patient and to the physician who is doing the examination.

Dr. J. Cash King, Memphis, Tenn. I think it would be worth while for Dr. Taylor to briefly outline some of the problems that will confront the users of radiant energies. Should laws be passed and a governing body set up to arrange licensing in the various states for individuals who use these radiant energies? I think that would be of great service to most in convincing the users of x-ray equipment that there is a definite advantage to them in their profession by taking the necessary precautions.

Dr. Taylor. There is not time to go into the subject of legislation at the present, other than to remark that, as many of you know, the Federal Government is setting up regulations with regard to the use of materials that it controls, namely, AEC produced materials. There are several states that have radiation regulations. Some of these regulations in their earlier proposed forms would have been extremely restrictive to the phyician in his use of x-rays in his usual practice. The National Committee has been wrestling with this problem for about three years, and a discussion of the problem, together with some suggested regulations which it is felt will be least restrictive to radiology and industry are published as National Bureau of Standards Handbook No. 61.

I think it is very important when the question of regulation and legislation comes up, that the medical groups get into the picture; that they not stand aloof from the question. If they do, and if they fail to go about the problem intelligently, they are very apt to find themselves working under unbearable restrictions. This is a thing that we have been very concerned about.

Dr. R. C. Boyer, Baton Rouge, La. Recently, we have been using film badges for all of our x-ray personnel, and we have been much disturbed by some of the reports that come back on our badges. The question that I have is, do you think that the quality of irradiation should be considered in regard to total body irradiation? It seems to me that in diagnostic work where we are using radiations of less than 100 or 130 K.V. there might be a different consideration than where one is considering body irradiation from radium, or some of the isotopes.

Dr. Taylor. My answer is definitely "yes." He is quite correct in implying that the radiation exposure from diagnostic procedures is low voltage. A large amount of it is absorbed in the skin where it will do

the least damage. On the other hand, there is a fairly high energy component of this scattered radiation which will go right straight through him, and it will leave behind a certain amount of absorbed radiation which contributes to his dose.

In considering genetic damage, the testes have practically no shielding at all, so it does not make much difference whether it is high energy or low radiation. In the case of the ovaries, they get a fairly substantial shielding from the soft radiations just by body tissue.

The safest plan, and it gives one a little safety factor, is to consider that all of the radiation that is incident on the body goes into the body, and that a substantial fraction of it is absorbed in the body. If one operates this way, knowing in fact that this is not quite the case, one will be providing himself with a small factor, or at times a fairly large safety factor.

The plain fact of the matter is, protection is very cheap. Protective devices for the equipment, shielding for the rooms, barriers for the operators, and so on, are extremely cheap in the diagnostic range, compared to the other expenses that are involved. It seems to me it would be "penny-wise and pound-foolish" to worry about the quality of radiation in a situation of this sort where the amount of lead, for example, that one has to put on a room, is usually the minimum amount that will hold itself together for handling a fraction of a millimeter. Many rooms will provide adequate shielding just because of their normal construction.

Generally speaking, one will find that the cheapest and most productive form of protection comes through improving the operating technics. One will find that if these are good, one does not need to worry much about costly barriers.

Medical Journalese?

I am going to start a one-man war against our chief occupational disease, though I cannot look forward to any Nobel award if I succeed. My only recompense will be the fact that the medical profession are the chief sufferers. Slowly but surely this detestable complaint, jargon aphasia, eporrhoea, or Herbert's disease, has been invading our ranks from the chief endemic reservoir of infection—the official circular. Typical cases, like the "disinfestation officer" who circulated a report which suggested that mice should be trapped as they emerge from their apertures, are fortunately rare, but there is no lack of this kind of thing:

"This failure to exercise objective acumen derives from professional indoctrination with the time-worn diagnostic axiom, that to seek a plurality of causes for a clinical picture is deplorable. It is understandable that in a busy clinic, scientific curiosity may be curbed when the therapeutic exigencies are abbreviated by the self-determined course of the disorder. . . . The phenomenology observed following ingestion of Datura stramonium seeds may be incorrectly interpreted as evidence of an affective disorder."

"Pronation deficiency following immobilisation in plaster can be minimised by taking care to avoid inversion of the foot, and to see that the foot is pronated in plaster as much as possible."

"The drug is devoid of risk, but irresponsible patients should preferably be institutionalised."

In the general presence of disease we may forget the look of health. "Sir, your son was struck in the leg by a cannonball, that we were forced to cut it off, whereof he died . . . " ". . . that you be hanged by the neck until you are dead, and the Lord have mercy on your soul." Deformed as we are, of necessity, by the weight of sulphonamides, heteroauxins, heteronymous hemianopias, and osteodystrophiae epiphysioarthriticae, we can at least raise our heads to look back at better days.

In the matter of words and units, the electricians, who made themselves a vocabulary to measure, have the better of us. Their terminology, crips, homely, and readily transferable into an alphabet of signs that recall gardening implements, is enviable to us—better than the rings and semi-detached indoxyl penthouses of the biochemists with their barbarous names. Could we not measure olfactory thresholds in snouts and megasnouts, the lateness of honorary physicians at rounds in dawdles or coffees? A terminology rugged but not barbarous, that is what we want. Let us take personal names if we wish, and to ohms and curies let us oppose chaplins of valgus deformity, potts of curvature, even megafreddies of azoospermia and charringtons of polyuria. We could well enrich the language which we are not occupied to outrage.

—Peripatetic Correspondent, *The Lancet*, 251:806 (Nov. 30) 1946.

Frequency of Cancer in the White and Negro: A Study Based Upon Necropsies

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This study contrasts not only the incidence of malignant lesions in the two races, but also analyzes the incidence as related to the organ systems.

Review of the Literature

THE EARLY OBSERVATIONS on the frequency of cancer in the white and negro races are of greater interest today from the historic than from the scientific standpoint. Hoffman[1] has said, "Previous to emancipation, the negro, by all the acceptable evidence available, was relatively much less subject to malignant tumors than the white race." The vital statistics from Charleston, South Carolina, between 1822 and 1848, showed 61, or 0.7 per cent, of 8,639 deaths in the white population, and 50, or 0.4 per cent, of 11,220 deaths in the negro population due to cancer.[2] Reyburn[3] studied the incidence of cancer between 1865 and 1872 in "freed people." In 430,466 cases of sick and wounded (mixed African races), there were 462 cases, or 0.1 per cent, due to cancer. In 18,027 deaths from all causes, only 62, or 0.3 per cent, were attributed to malignant tumors.

In 1896, a study of the frequency of cancer in different races was made in New Orleans, Louisiana, by Matas;[4] he concluded that "mesoblastic derivatives of the embryonal connective tissue type, i.e., the sarcomata, are also apparently more frequent in the negro, with the sole exception of the melanotic sarcomas, which are rare." This investigator suggested that the constitution of the Negro probably had undergone some change under the conditions of American civilization, since "it cannot be doubted that cancer is comparatively rare in the native African, rare also in the original slave population of this country, and has only become a common disease in the American Negro of the last few generations."

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Hoffman,[5] in 1915, said "without exception the general cancer mortality is higher for the white population than the negro."

In 1927, Pearl and Bacon[6] found that cancer was more frequent in the white race than in the negro in the autopsies at Johns Hopkins Hospital in Baltimore. Quinland and Cuff,[7] in 1940, found cancer in 7.5 per cent of 813 autopsied cases in Negroes at a Nashville, Tennessee hospital. Steiner,[8] in 1954, found malignant tumors in 12.7 per cent of 2,236 autopsies in Negroes in Los Angeles, California. It is of interest to know that the frequency of cancer, as observed at autopsy, has varied in different studies.

In 1950-52, the United States Public Health Service[9] reported a study on cancer morbidity in ten major cities. Eight of the ten cities showed a lower cancer rate for non-whites than for whites, even where cancer of the skin was disregarded. In New Orleans, Louisiana, there was no difference between the over-all cancer rate for the white and non-white; however, in the frequency of cancer in specific anatomic sites, a difference was found in the two groups.

Statistical studies indicate the need to establish the frequency of the occurrence of cancer in specific sites within the body in order to learn whether there is a significant variation in the frequency of cancer in the white and non-white population. Cancer of the skin is generally accepted to be more common in the white than in the Negro; however, Schrek[10] points out that cancer of the exposed skin (face, ears, neck, hands and wrists) is more frequent in whites than Negroes, but cancer of the covered skin (scalp, trunk, arms, legs and feet) has the same incidence in the two races. In the white race, cutaneous cancer is more prevalent in the South; in the negro

race the incidence of cutaneous cancer is not affected by geographic factors.

At Vanderbilt University Hospital in Nashville, Tennessee, McSwain and Williams[11] observed that cancer of the cervix, breast and stomach is relatively more frequent in Negroes than in whites; cancer of the fundus of the uterus is approximately the same, but cancer of the lung is relatively more frequent in the white than in the negro patients. Malignant tumors of the brain and spinal cord are much more common in the white race than in the negro. Dublin[12,13] has pointed out that cancer of the buccal cavity is less common among negro males than white males; from 1931 to 1935 cancer of the stomach and liver was higher in the white than in the negro race,[12] while from 1941 to 1945 it was essentially the same between the two races.[13] Cancer of the female generative organs is more frequent in the Negro than in the white.[12,13] Steiner[8] recently made a detailed study of cancer in the autopsies at Los Angeles County Hospital. From this he concluded, "It appears then, to be established that the cancer frequency is less in the Negroid than the Caucasoid. This is not to be interpreted as a proved genetical manifestation. While it may be such, the probability exists that it is not." Steiner[8] suggested that at least part of the difference in the frequency of cancer, as reported by Pearl and Bacon,[6] Dorn,[14] Dublin,[12] Gover,[15] and in his own study, may be "explained by clinical underdiagnosis in Negroes."

Present Study

Rigdon and associates,[16] in 1952, reported on the frequency of cancer in the white and negro races as observed at autopsy. It was noted that the peak of frequency in the malignant tumors occurred from 50 to 59 years of age in the negro female, 10 years later than it did in the white female. It occurred from 50 to 59 years of age in the negro male, 10 years earlier than in the white male. The peak of cancer frequency occurred at the same age in both negro male and female; however, in the white male and female there was a 20 year variation. The percentage of malignant tumors in both the negro male and female was lower than that in the white male and female. The necessity was pointed out by Rigdon and associates[16] for a study of the specific types of cancer occurring in the two races in the different anatomic sites of the body. The present paper is a report of the types of cancer found in whites and Negroes, 20 years of age and over, in 6,575 consecutive necropsies, studied between January 1, 1920, and December 31, 1954, at the John Sealy Hospital in Galveston, Texas. Thirty-nine additional autopsies were performed during these 34 years, but because of incomplete records they are not included in this study.

The number of autopsies, the number and the percentage of cases of cancer in whites and Negroes, for each decade of life, are shown in table 1. In these data, cancer is found in 24.4 per cent of the autopsies in whites and 16.8 per cent of the autopsies in Negroes. When tested for statistical significance, this difference is highly significant ($P = < .01$). In the 6,575 autopsies there are 1,392 cases of cancer. Table 2 shows the distribution of the cancer cases in the white and in the Negro by anatomic site. There are significantly more cases of cancer in the central nervous system, respiratory tract, biliary tract, reticulo-endo-

TABLE 1

NUMBER OF AUTOPSIES, THE NUMBER AND THE PERCENTAGE OF CASES OF CANCER IN WHITES AND NEGROES, ACCORDING TO AGE GROUP, FOUND IN THE 6,575 AUTOPSIES PERFORMED AT JOHN SEALY HOSPITAL BETWEEN JANUARY 1, 1920, AND DECEMBER 31, 1954

Age	*20-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*	*Unknown*	*All ages*
Autopsies								
White	338	435	664	814	770	656	83	3760
Negro	330	517	627	577	429	285	50	2815
Cases—Cancer								
White	27	58	154	230	252	188	10	919
Negro	25	41	86	132	101	86	2	473
Per cent—Cancer								
White	8.0	13.3**	23.2**	28.3*	32.7**	28.7	12.0	24.4**
Negro	7.5	7.9	13.7	22.9	23.5	30.2	4.0	16.8

*P=<.05 **P=<.01

TABLE 2

NUMBER AND PER CENT DISTRIBUTION OF THE 1,392 CANCER CASES IN THIS SERIES OF AUTOPSIES BY RACE AND ANATOMIC SITE

Distribution—Cancer by Site	*No. Cases Cancer*		*Per cent—Autopsies*		*Per cent—Cancer*	
	White	*Negro*	*White*	*Negro*	*White*	*Negro*
G. I. tract	187	129	5.0	4.6	20.3	27.3**
Genital tract	125	95	3.3	3.4	13.6	20.1**
Respiratory tract	137	39	3.6**	1.4	15.0**	8.2
Biliary tract	108	58	2.9*	2.1	11.7	12.3
Cent. Nerv. Syst.	108	15	2.9**	0.5	11.7**	3.2
Urinary tract	53	29	1.4	1.0	5.8	6.1
Leukemia	49	20	1.3*	0.7	5.3	4.2
Misc.—Unknown	39	28	1.0	1.0	4.2	5.9
R. E. system	43	17	1.1*	0.6	4.7	3.6
Breast	20	21	0.5	0.7	2.2	4.4*
Skin	22	6	0.6*	0.2	2.4	1.3
Endocrine glands	19	6	0.5	0.2	2.1	1.3
Skeletal	9	10	0.2	0.4	1.0	2.1

*P=<.05 **P=<.01

thelial system, skin, and blood (leukemia) in the autopsies in the whites than in the autopsies in the Negroes, as shown in this table.

The relative frequency of cancer in all autopsies in white and negro males is shown in table 3. Of the white males, 24 per cent have cancer and of the negro males, only 18 per cent. This difference in frequency is highly significant (P=<.01). However, when the frequency is determined for the different age groups, only the decades 40 to 49 and 60 to 69 show a significant variation in favor of the whites (P=<.01).

The distribution of all cancers in males by race and site is shown in table 4. The percentage of gastrointestinal tumors found in the white male autopsies and the negro male autopsies is the same for both races. There is, however, a highly significant difference in the cancer to autopsy ratio between the white and negro males for tumors found in the respiratory tract and the central nervous system. Of the autopsies on white males, 4.4 per cent were found to be tumors of the respiratory tract and 2.4 per cent tumors of the central nervous system; corresponding figures for the negro male are 1.9 per cent and 0.6 per cent. In these data, there is a significantly (P=.02) greater amount of cancer of the urinary tract in white males than negro males, 1.6 per cent to 0.9 per cent. Cancer of the male genital tract is more common (P=.03) in the negro male than the white male, 3.4 per cent to 2.3 per cent. Of the white male cancer cases, 23.2 per cent are found in the gastrointestinal tract and 31.4 per cent of the negro male cancer cases are present in the gastrointestinal tract. Cancer of the respiratory tract constitutes 18.8 per cent of the cancers found in the white male and 10.2 per cent of those found in the negro male. Cancer of the genital tract was found in 9.8 per cent of the cancer cases in the white male and 18.3 per cent of the cancer cases in the negro male. Three per cent

TABLE 3

NUMBER OF AUTOPSIES, THE NUMBER AND PERCENTAGE OF CASES OF CANCER, ACCORDING TO AGE AND RACE, IN THE MALE

Age	*20-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*	*Unknown*	*All ages*
Autopsies								
White male	190	289	473	661	613	497	68	2791
Negro male	152	273	387	372	317	207	34	1742
Cases—Cancer								
White male	16	32	93	174	198	142	9	664
Negro male	13	22	50	89	76	72	0	322
Per cent—Cancer								
White male	8.5	11.1	19.7**	26.3	32.3**	28.5	13.2	24.0**
Negro male	8.6	8.1	12.9	23.9	24.0	35.0		18.0

**P=<.01

TABLE 4

NUMBER AND PERCENTAGE OF CANCER CASES, IN SPECIFIC ANATOMIC SITES, ACCORDING TO RACE, OF THE 986 CANCER CASES IN MALES

Distribution—Cancer by site	*No. Cases Cancer*		*Per cent—Autopsies*		*Per cent—Cancer*	
	WM	*NM*	*WM*	*NM*	*WM*	*NM*
G. I. tract	154	101	5.5	5.8	23.2	31.4**
Genital tract	65	59	2.3	3.4*	9.8	18.3**
Respiratory tract	125	33	4.4**	1.9	18.8**	10.2
Biliary tract	77	41	2.8	2.3	11.6	12.7
Cent. Nerv. Syst.	66	10	2.4**	0.6	9.9**	3.0
Urinary tract	46	15	1.6*	0.9	6.9	4.7
Leukemia	38	18	1.4	1.0	5.7	5.6
Misc.—Unknown	24	16	0.9	0.9	3.6	5.0
R. E. system	29	14	1.0	0.8	4.4	4.3
Breast	2	0	0.1		0.3	
Skin	18	5	0.6	0.3	2.7	1.6
Endocrine glands	14	5	0.5	0.3	2.1	1.6
Skeletal	6	5	0.2	0.3	0.9	1.6

*P=<.05 **P=<.01

of the cancers found in the negro male are central nervous system tumors, while the corresponding figure for the white male is 9.9 per cent.

The relative frequency of cancer in the autopsies in the white and negro female is shown in table 5. Cancer is found in 26 per cent of the autopsies on white females and 14 per cent of the autopsies on negro females. This difference is statistically significant at all age groups except the third decade.

The anatomic site and race of the 406 cancers in the female are given in table 6. The cancer to autopsy ratio is higher in the white female than in the negro female in the following sites: genital tract, biliary tract, central nervous system, blood (leukemia), reticulo-endothelial system and endocrine glands. The highest percentage of the cases of cancer is found in the genital tract in both races. Tumors of the central nervous system are found in 16.2 per cent of the cancer cases in the white female, while the percentage for the negro female is only 3.3. Cancer of the breast is more common among the cancer cases found in the negro female than those found in the white female.

Table 7 shows the age, sex, race and number of cases present in specific anatomic sites. In this series, the number of tumors of the central nervous system in the white male in the age group 40 to 49 is highly significant when compared with the number occurring in the negro male in the same age group. The difference in the number of respiratory cancers between the white male and the negro male is statistically significant, in favor of the white, only at 50 to 59 years of age. There is more cancer of all sites found in the white male than in the negro male in the age group 60 to 69 (Table 3) but the difference is not significant at any particular site. Tumors of the central nervous system are more common in white females than negro females in the

TABLE 5

NUMBER OF AUTOPSIES, THE NUMBER AND PERCENTAGE OF CASES OF CANCER, ACCORDING TO AGE AND RACE, IN THE FEMALE

Age	*20-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*	*Unknown*	*All ages*
Autopsies								
White female	148	146	191	153	157	159	15	969
Negro female	178	244	240	205	112	78	16	1073
Cases—Cancer								
White female	11	26	61	56	54	46	1	255
Negro female	12	19	36	43	25	14	2	151
Per cent—Cancer								
White female	7.4	17.8**	31.9**	36.6**	34.4*	29.0*	6.7	26.0**
Negro female	6.7	7.8	15.0	21.0	22.3	18.0	12.5	14.0

*P=<.05 **P=<.01

TABLE 6

NUMBER AND PERCENTAGE OF CANCER CASES, IN SPECIFIC ANATOMIC SITES, ACCORDING TO RACE, OF THE 406 CANCER CASES IN FEMALES

Distribution—Cancer by site	*No. Cases Cancer*		*Per cent—Autopsies*		*Per cent—Cancer*	
	WF	*NF*	*WF*	*NF*	*WF*	*NF*
G. I. tract	33	28	3.4	2.6	13.0	18.5
Genital tract	60	36	6.2**	3.3	23.5	23.8
Respiratory tract	12	6	1.2	0.6	4.7	4.0
Biliary tract	31	17	3.2*	1.6	12.2	11.3
Cent. Nerv. Syst.	42	5	4.3**	0.5	16.2**	3.3
Urinary tract	7	14	0.7	1.3	2.7	9.3**
Leukemia	11	2	1.1**	0.2	4.3	1.3
Misc.—Unknown	15	12	1.5	1.1	5.9	7.9
R. E. system	14	3	1.4**	0.3	5.6	2.0
Breast	18	21	1.8	1.9	7.1	13.9*
Skin	4	1	0.4	0.1	1.6	0.7
Endocrine glands	5	1	0.5*	0.1	2.0	0.7
Skeletal	3	5	0.3	0.5	1.2	3.3

*P=<.05 **P=<.01

age groups 20 to 29, 30 to 39 and 50 to 59. While in our series there is more cancer among white females than negro females at all ages except 20 to 29 (Table 5), we do not find a statistically significant difference at any specific site other than the central nervous system.

The per cent distribution of the 1,392 cancer cases in individuals 20 years of age and older by site, sex and race is shown in figure 1. The percentage of tumors of the respiratory tract in the colored male is less than found in the gastrointestinal tract, genital tract and biliary tract, but in the white male only the

TABLE 7

NUMBER OF CANCER CASES IN SPECIFIC ANATOMIC SITES BY SEX, RACE AND AGE

Age	*Sex and Race*	*G. I. Tract*	*Genital Tract*	*Resp. Tract*	*Biliary Tract*	*Cent. Nerv. Syst.*	*Urinary Tract*	*Leukemia*	*Misc. Unknown*	*R. E. System*	*Breast*	*Skin*	*Endocrine Glands*	*Skeletal*
20 to 29	WM	3	0	0	0	4	0	2	1	3	0	0	3	0
	NM	3	0	1	3	1	1	2	1	0	0	1	0	0
	WF	0	2	1	1	5*	0	1	1	0	0	0	0	0
	NF	1	2	0	0	0	2	0	5	0	1	0	0	1
30 to 39	WM	6	0	5	3	8	1	2	3	4	0	0	0	0
	NM	8	1	0	2	2	0	4	2	1	0	1	0	1
	WF	1	8	2	0	11**	0	2	1	0	0	1	0	0
	NF	3	6	0	1	0	1	0	1	2	5*	0	0	0
40 to 49	WM	16	0	25	11	17**	3	8	2	7	0	1	3	0
	NM	15	4*	10	5	1	3	1	2	5	0	1	2	1
	WF	5	16	1	3	14	0	4	3	6	5	0	3	1
	NF	10*	12	1	2	2	1	0	1	0	5	0	1	1
50 to 59	WM	37	11	36**	20	20**	10	14	6	6	0	10	2	2
	NM	28	10	9	14	2	6	5	4	5	0	1	3	2
	WF	3	18	1	7	9**	3	1	3	3	6	1	1	0
	NF	4	11	2	7	0	7	1	2	0	7	0	0	2
60 to 69	WM	53	18	38	24	14	21	4	7	6	1	5	4	3
	NM	29	14	8	12	1	2	4	4	2	0	0	0	0
	WF	8	9	5	13	2	3	1	4	2	5	1	0	1
	NF	6	4	2	3	2	1	0	1	1	3	1	0	1
70 +	WM	34	36*	19	19	2	11	7	5	3	1	2	2	1
	NM	18	30	5	5	3	3	2	3	1	0	1	0	1
	WF	16	7	2	7	1	1	1	3	3	2	1	1	1
	NF	4	0	1	4	0	2	1	2	0	0	0	0	0
Unk.	WM	5	0	2	0	1	0	1	0	0	0	0	0	0
	WF	0	0	0	0	0	0	1	0	0	0	0	0	0
	NF	0	1	0	0	1	0	0	0	0	0	0	0	0

*P=<.05 **P=<.01

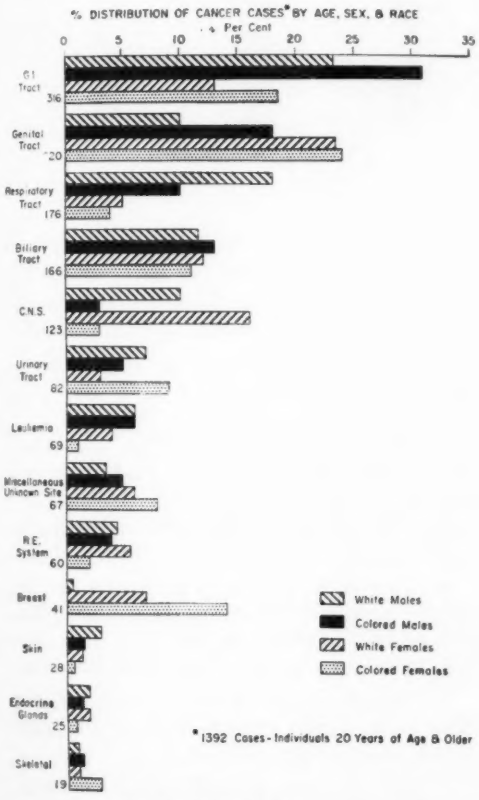
percentage of tumors found in the gastrointestinal tract is larger than that in the respiratory tract.

Figure 2 shows the per cent distribution of these cancer cases by age, sex and race. This graph shows very nicely the difference in the percentage of cancer between the white and negro female in each age group. The percentage of cancer found in the white male decreases at 70 years of age and over and increases in the negro male.

The percentage of cancer, covering five year periods, for each sex and race, is shown in figure 3. In these data, the rise in the percentage of cancer cases in the white male is not statistically significant until the years 1945 to 1950, at which time there is an increase over the preceding five years, and again in 1950 to 1955, a significant increase occurs over 1945 to 1950 ($P = < .01$). In the negro male, there is a significant increase during 1940 to 1945 over 1935 to 1940 ($P = < .05$), none in 1945 to 1950, but a highly significant increase in the years 1950 to 1955 ($P = < .01$).

In the autopsies on the white female, the first significant increase in the percentage of cases of cancer is during 1940 to 1945 ($P = < .05$), with a highly significant increase during 1950 to 1955 ($P = < .01$). In the negro female, there is a significant increase in the percentage of cancer cases between 1945 and 1950 ($P = < .05$); however, there is no significant increase from 1950 to 1955 over the preceding five years.

FIG. 1



The per cent distribution of the 1,392 cancer cases in the 6,575 autopsies performed on individuals 20 years of age and over by site, sex and race.

Discussion

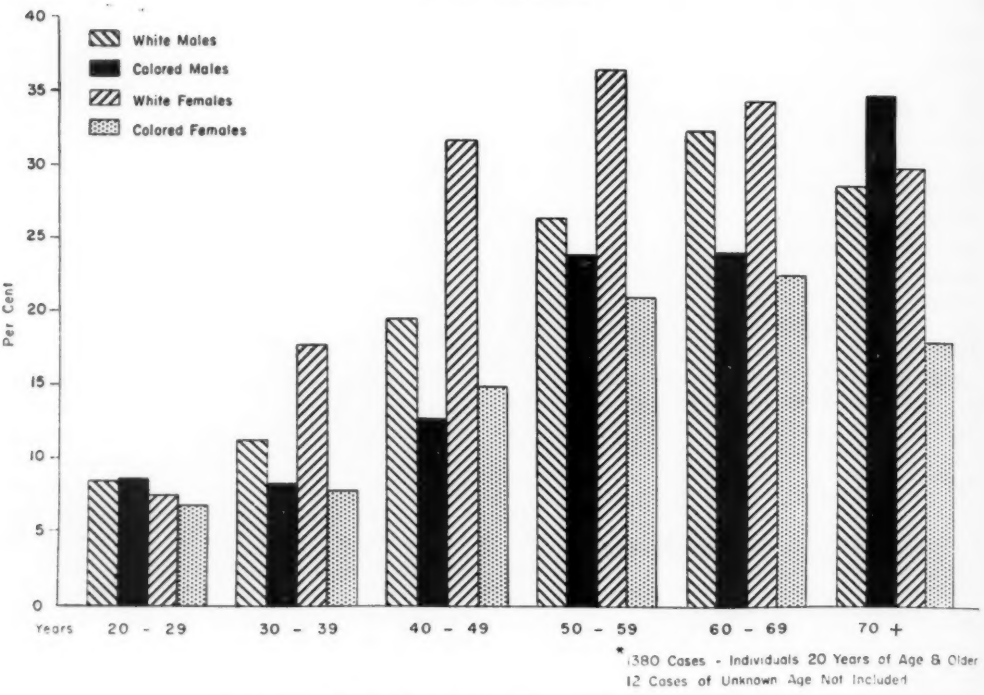
The limitations of statistical data obtained from autopsies are well recognized; however, such studies may contribute to the over-all problem of cancer. This study is based upon 6,575 consecutive autopsies, on individuals 20 years of age and older, observed at Galveston, Texas, during a period of 35 years (1920 through 1954). There were 1,392 cases of cancer. The percentage of cancer cases in this autopsy series has progressively increased since 1920, as shown in figure 3. However, apparently the increase is not statistically significant until 1940 to 1945. In cancer statistics 1940 may be a significant period since this marks the time when infectious diseases were first being brought under therapeutic control through the use of antibiotics. These data may also be significant in statistics of cancer of the lung; 1939 was the first year this neoplasm was recorded as a specific disease entity.[17] The increase in the number of recorded cases giving cancer of the lung as the cause of death has been phenomenal since 1940.

The percentage of cancer deaths in the white race is significantly greater ($P = < .01$) than that in the negro race in this series of autopsies. These data also show that the frequency of cancer in the white male is significantly ($P = < .01$) greater than that in the negro male; too, the frequency of cancer in the white female is significantly ($P = < .01$) greater than in the negro female. Although the total number of cases of cancer occurring in specific anatomic sites is small in this study, the following specific conclusions would seem to be justified:

FIG. 2

% DISTRIBUTION OF CANCER CASES*

BY AGE, SEX, & RACE



The per cent distribution of the 1,392 cases of cancer by age, sex and race.

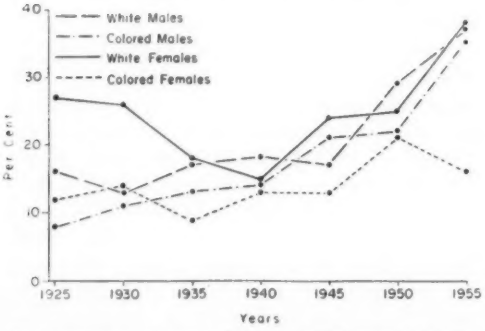
1. The percentage of tumors found in the gastrointestinal tract is the same for the male in both races.

FIG. 3

% CANCER IN AUTOPSIES

FOR 5 YEAR PERIODS ACCORDING TO SEX & RACE

Individuals 20 Years of Age & Older



The percentage of cases of cancer, based upon five-year periods, found in the autopsies on individuals 20 years of age and older at the John Sealy Hospital between January 1, 1920, and December 31, 1954, according to sex and race.

2. There is no significant difference in the percentage of tumors found in the gastrointestinal tract in the white and negro female.

3. The percentage of central nervous system tumors is greater in the white than it is in the Negro.

4. The over-all percentage of respiratory tract tumors is significantly higher in the white male than in the negro male; however, in specific age groups, the difference is statistically significant only at 50 to 59 years of age.

5. Cancer is significantly greater in the biliary tract, reticulo-endothelial system, skin and blood (leukemia) in the white race than it is in the negro, in this group of autopsies.

6. Cancer of the breast is more frequent among the cancer cases found in the negro female than in the white female.

7. Cancer of the genital tract is statistically more frequent in the Negro than in the white.

In this study cancer of the central nervous system is more frequent in the white than in the Negro; McSwain and Williams[11] also found malignant tumors of the brain and spinal cord more frequent in the white than in the Negro. The observation that cancer of the lung is more frequent in the white than in the Negro is in agreement with a previous study,[18] with that of McSwain and Williams[11] and also that of Pearl and Bacon.[6] It differs, however, with that of Steiner[8] who found no significant difference in the frequency of carcinoma of the lung between Caucasians, Negroes and Japanese in the Los Angeles autopsy data compiled in 1954.

Many of the published observations[11-14] on the frequency of cancer in the white and Negro support the opinion that cancer is more frequent in the white. There does seem to be a need for further study on the frequency of cancer in the two races referable to specific anatomic sites since there is now an observed variation in the frequency of the occurrence of cancer in specific sites.[8,11,14]

Summary

A study of the frequency of cancer in the autopsies performed between 1920 and 1954 in the John Sealy Hospital shows that cancer occurs more frequently in the white than in the Negro. Although the number of cases occurring in specific anatomic sites is small in this series of autopsies, the following conclusions may be drawn:

1. The percentage of tumors found in the gastrointestinal tract is the same for whites and Negroes.

2. The percentage of central nervous system tumors is greater in the white than it is in the Negro.

3. The percentage of respiratory tract cancers in specific age groups is significantly higher in the white male only between 50 and 59 years of age.

4. Cancer is significantly greater in the biliary tract, reticulo-endothelial system, skin and blood (leukemia) in the white than it is in the Negro in this series of autopsies.

5. Cancer of the breast is more frequent among the cancer cases found in the negro female than those in the white female.

6. Cancer of the genital tract is statistically more frequent in the negro than it is in the white race.

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Wilm's Tumor*

GERALD H. TEASLEY, M.D.,† *Texarkana, Ark.-Tex.*

The prognosis in the Wilm's tumor, though apparently improving, is still gloomy. The author offers a plea for a cooperative study among urologists in the hope of learning what course of management offers the best in prognosis.

THE ONLY STATEMENT which can be made concerning Wilm's tumor that is common to all reports is "the problem presented has not been solved." It was hoped that a fairly comprehensive review of writings might reveal a method of treating these tumors which could be of benefit to the patient. Unfortunately, the confusion found when comparing the statistics of many authors could not be dissipated. Some reports are incomplete in regard to treatment. Surveys, and surveys of other surveys demonstrate that each author started the study with a different idea in mind and developed that facet of personal interest. As a result this study has not been a source of proven progress. However, a question has been brought forward in regard to postoperative irradiation which is not in agreement with practically all conclusions heretofore made, but should give us pause in order to re-evaluate our present thinking.

Let us review briefly certain known facts concerning Wilm's tumor. It is occasionally seen in adults but over 80 per cent of all cases are found in children below eight years of age. It has been diagnosed in infants less than three days of age. A report is available of its occurrence in identical twins, one in the right, the other in the left kidney. No report of a spontaneous regression of the tumor was found. It is the second most common malignancy of childhood. In the past, the survival rate has been less than 10 per cent. Fortunately, a definite improvement has been seen in the five year survivals during the past two decades. However, it is not uncommon to read articles by excellent urologists who report several cases each with no five year survival. This is indeed a most regrettable fact and one that should be remedied if humanly possible.

Recurrences after treatment usually appear in less than 18 months but there are reports of recurrence over 40 months after removal of the tumor. We can assume that if a child lives beyond the first 18 months, the chances of a five year survival are markedly increased. It has also been shown that the chance of survival in cases diagnosed before 18 months of age is much greater than in older children.

Diagnosis

The most important diagnostic finding is a mass in the flank. We know that many children are brought to the physician because a mass was felt by the mother or nurse at the time of bathing. We also know that the mass may appear fairly suddenly due to hemorrhage within the pre-existing tumor. Enlarged veins may be seen over the abdominal wall. Fever is common, as is nausea, loss of appetite, and some listlessness. Hematuria is not encountered often.

X-ray findings are extremely important. A scout film of the abdomen followed by an excretory urogram often assures the diagnosis. Angled films are a great help in associating a tumor mass with the kidney. There are no typical x-ray deformities of a Wilm's tumor but their value suggesting the diagnosis cannot be minimized. In the event excretory urography is not sufficient to outline treatment, one should not hesitate to make retrograde pyelograms. Calcification in the tumor mass is thought to be a favorable sign in prognosis.

Other conditions to be considered while doing the usual diagnostic procedures are suprarenal tumors, hydronephrosis, polycystic disease, splenomegaly, hepatomegaly, pancreatic cysts, retroperitoneal tumors and a psoas abscess. These can usually be eliminated in the process of examination.

Treatment

Treatment is concerned with two proce-

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dures,—surgery and irradiation. From statistical reports, confusing as they are, more cases have been treated by surgery alone than by any other method and, as a result, more cases of five year survivals are included in this group.

The most popular incision seems to be the transperitoneal approach with either a longitudinal, transverse or T-incision according to the desires of the operating surgeon. Some urologists prefer an ample loin incision and others a thoracico-abdominal approach. The important technical consideration is to expose the renal pedicle first, ligate the vessels and thus attempt to prevent dislodging tumor cells into the general circulation while freeing the tumor from surrounding tissues.

Preoperative irradiation is condemned by some and used routinely by others. The chief objection to its use has been the waiting period referred to as 4 to 6 weeks. Such a waiting period is not necessary. In cooperation with our radiologist, two patients have received 1,500 r of irradiation in 7 days followed immediately by operation. Due to the extreme sensitivity of the tumor cells to irradiation, a very rapid and remarkable decrease in the size of the tumor can be expected. Thus the waiting period for surgical treatment following irradiation does not have to be 4 to 6 weeks. Shrinkage of the tumor after irradiation may make an inoperable tumor operable. This type of irradiation is not intended to be a curative procedure but is an important adjunct to surgical removal of the mass alone.

Irradiation alone has been followed by five year survivals. An author who treated 20 cases with this procedure does not advocate its use. However, it is recommended for those cases with metastasis or those with recurrences following metastasis. Burns, of New Orleans, in a personal communication, also uses nitrogen mustard with irradiation for treatment of recurrences. Perhaps this might be applicable in other cases also.

To assist in obtaining the latest information, several urologists throughout the country were written letters. In their replies they were unanimous in recommending postoperative irradiation for these cases. This is in agreement with the reports in the literature. However, as mentioned earlier, a question concerning postoperative irradiation has clouded my thinking. The following quotation from an article certainly is poor reason (without criticism to the author intended) for giving postoperative irradiation. "It can be said for postoperative irradiation that it does no harm, since surgery is not postponed by its use, also, it gives the surgeon and the family the comfortable feeling that all possible has been done to save the life of the child."

This type irradiation is not without its dangers. One author reported three cases of radiation nephritis of the remaining kidney with immediate death in two. The damage done to the other soft tissues and bones cannot be accurately determined. To treat all possible metastatic sites would require general body irradiation which is completely impractical. With this in mind, and a questionable trend in the statistics to support this view, does it not appear possible that postoperative irradiation is not necessary? This is assuming that the tumor is removed intact, no evidence of local invasion is found and no lymph nodes are palpable. I believe, to help clarify this problem, it would be wise to request a central agency to send out questionnaires to all urologists asking for information concerning the number of patients treated, age, signs of local invasion, the type of treatment and the survival figures. From such a survey, one could more definitely determine the value of postoperative irradiation for Wilm's tumors. I must assure you that the above statements are made with the realization that they conflict with many reports in the literature. I do not recommend operation without postoperative irradiation as the treatment of choice, but I do say we have not definitely proven it is not the treatment of choice in those cases with no evidence of spread beyond the tumor mass.

Very briefly, I would like to present two cases of Wilm's tumor. As an unusual coincidence they were both referred to me by the same physician.

Case Reports

Case 1. An 11 months old infant. The mother had found a mass in the left side while dressing the baby, two days previously.

The mass filled the entire left abdomen and was not tender. An excretory urogram showed a normal kidney on the right; the left calyceal system was distorted and a large soft tissue mass was seen. Preoperative irradiation was given (1,500 r in 7 days). Through a left rectus incision, a transperitoneal approach to the left kidney was accomplished. After tying the

renal pedicle, the mass was removed. No postoperative irradiation was used. This child is well and healthy 22 months postoperatively.

Case 2. A 10 months old infant. The father noticed a lump in the left side one week previously.

The mass filled the entire left abdomen from below the symphysis to above the costal margin. An excretory urogram showed a normal right kidney; on the left, a large soft tissue mass was present. The calyceal system was markedly distorted. After irradiation, the mass had decreased to less than one-half its former size. Through a left rectus, transperitoneal incision, the renal pedicle was isolated and the vessels ligated. The mass was then removed without difficulty. Postoperative irradiation was not prescribed. This child is doing well five months postoperatively.

Neither of these cases can possibly satisfy the requirements for a cure. The chances in the first are excellent and in the second unknown. Perhaps both should have received postoperative irradiation but with no evidence of local involvement, I agreed with our local radiologist who asked "what shall I irradiate?"

Summary

1. The literature on Wilm's tumor is reviewed briefly.

2. Analysis of statistical reports is quite confusing.

3. Patients having a Wilm's tumor have an extremely poor prognosis but definite trends for the better are seen.

4. Treatment should be instituted as soon as practical. Surgery combined with irradiation is our best weapon at present. Postoperative irradiation is advised by most authors but a question is raised as to its necessity in all cases.

5. Metastasis or recurrences should be treated by irradiation. Nitrogen mustard has also been advocated.

I should like to express appreciation to Drs. Edgar Burns, New Orleans, La., Reid Nesbit, Ann Arbor, Mich., Rubin H. Flocks, Iowa City, Ia., Roger W. Barnes, Los Angeles, Calif., Harry M. Spence, Dallas, Tex., Meredith Campbell, New York City, N. Y., and James H. DeWeerd, Rochester, Minn., for their kindness in replying to a questionnaire concerning this problem.

The references to the papers consulted in arriving at the conclusions in this paper will appear in the author's reprints.

Discussion (Abstract)

Dr. Irving Victor, Savannah, Ga. I would like to congratulate Dr. Teasley on a very lucid presentation of a very fascinating problem.

I am both delighted and flattered to discuss this paper for it is one subject in urology on which I feel that I may speak authoritatively, in the light of my vast series of 2 cases. I am reminded of the young doctor who was called on for his opinion of a distressing and serious problem which happened to be Wilm's tumors. His predecessors in the discussion, older and wiser heads, had bemoaned the fact that their results were poor at best. He rose to his feet and stated that he had never had any difficulty with Wilm's tumors and then added, "perhaps that is because I have never seen a Wilm's tumor."

I have been interested in Wilm's tumors in spite of the paucity of my clinical material. However, I have had the opportunity to see a fairly sizable group of these cases while in Minnesota and to follow them for a period of time.

The major concern of the urologist is in the adequate management of these cases, after the diagnosis has been definitely established. This management may be arbitrarily divided into three stages,—preoperative, operative, and postoperative. Let us first consider the preoperative management.

Dr. Teasley recommends preoperative irradiation for 7 days which is then followed by surgery. He feels that if operation is done by the end of the first week it makes for an easier procedure and even may make an inoperable tumor operable. True, this facilitates the technical aspect of the operation but does it not offer the risk of softening or even liquifying tumor cells and permitting them to break off into the circulation? Secondly, postponing operation for even a week would seem unwarranted if the tumor can be removed successfully in spite of the size. Gross, of Boston, feels these patients should be treated as surgical emergencies and that preoperative irradiation should be used only when it is felt that one cannot remove the tumor without it. In 1949, Gross gave alternate patients with a Wilm's tumor 2,000 to 3,000 roentgens over the tumor mass and then operated; within a year it became evident that the fatality rate of those receiving irradiation was rising sharply and they felt that such irradiation before operation was detrimental and therefore it was abandoned.

As has been pointed out, in my opinion, these cases should be treated almost as surgical emergencies. Certainly repeated palpation of the presenting mass should not be permitted for this increases the chance of massaging tumor cells into the circulation. The sooner the tumor mass is excised the better are the chances for cure. Dr. Teasley has given an excellent presentation of the technical difficulties involved at operation, and I would like to re-emphasize the importance of early ligation of the vascular pedicle so that tumor cells will not be dislodged into the general circulation while freeing the tumor mass.

As for the postoperative irradiation, a problem certainly arises. Almost 9 months ago I removed a large Wilm's tumor from a 5 month old white girl. A transperitoneal approach was used and the tumor was removed cleanly. Our radiologist felt nothing would be gained by irradiation and possible epiphyseal damage might result. In reviewing all of his cases from 1940 through 1947, Gross points out that his cure rate was definitely raised by postoperative irradiation. He feels

that even though the tumor is enucleated cleanly, in some cases tumor cells are left behind which cannot be seen with the naked eye. It is in this type of case that irradiation may help by effectively killing these tumor cells. His group now routinely uses postoperative irradiation. Treatment should be started on the day of operation and a total of 4,000 to 5,000 roentgens should be given over the renal fossa. This assumes, of course, that there are no distant metastases. If there are isolated metastatic lesions in the lungs and no evidence of widespread disease, it is probably desirable to treat them intensively and repeatedly.

The feeling of pessimism and hopelessness expressed by so many men who have handled these cases should be dispelled. Increasing percentages of cures have certainly given much hope to a heretofore gloomy situation.

Weisel, Dockerty and Priestly reported a 14 per cent cure rate, in 1943. In 1946, Nesbit and Adams reported a 50 per cent cure rate. Silver, in 1947, reported 18 cases with 10 survivals, or a 55 per cent cure rate, but 2 of these cases were in adults and no uniform treatment was instituted. Dickey and Chandler, in 1949, reported 12 cases with 4 survivals, or a 33 per cent cure rate. Gross, at Boston Children's Hospital, reported a study of all cases from 1914 to 1947. The following is the breakdown of cases: 1914 to 1930, 27 cases with 4 cures, or a 14.9 per cent cure rate; 1931 to 1939, 31 cases with 10 cures, or a 32.2 per cent cure rate; 1940 to 1947, 38 cases with 18 cures or a 47.3 per cent cure rate. He attributes the rise in cure rate to the routine use of postoperative irradiation over the renal fossa.

I should again like to congratulate Dr. Teasley for a most interesting and stimulating paper.

Dr. Douglas E. Scott, Lexington, Ky. We are all of us grateful to hear from Dr. Teasley that there is a meaningful improvement in survival rates in reports of the past two decades. If this is due in any way to the management of the disease I would consider it in largest part the result of very obvious betterment in surgical technic which has taken place in that period. We have learned that we must approach this tumor as we would a time bomb and tie the pedicle as we would remove the fuse, first and with all the delicacy of which we are capable. This in no way diminishes the importance of the x-ray therapy for the great sensitivity of the tumor to radiation has not changed.

Dr. Teasley has wisely tried not to be dogmatic in his suggestions regarding any form of treatment. Of course, none of us can be with perhaps a hundred or so recorded survivals in the literature.

The essayist recognizes the wisdom of postoperative irradiation on a percentage survival basis and at the same time questions its universal necessity. With that thesis I can readily agree. However, I find myself reluctant to put it all into practice. I cannot feel that mere absence of visible extension of the disease at time of operation is a safe criterion. The best of surgical technics is indelicate enough to possibly seed some tumor cells. If I am haunted by a fear of microscopic metastases, I have my small reasons. Six patients were operated upon in my community by understanding surgeons and had no evidence of extension beyond the kidney. Four were just as quickly dead of the disease as if the extension had been visible. One who had postoperative x-ray was apparently well 11 months later. If Dr. Teasley's cases eventually survive their disease it will be a tribute to meticulous surgical manipulation. Certainly he is to be congratulated on their survival thus far.

In any discussion of the merits of x-ray therapy, pre- and postoperative treatment cannot be considered as separate entities having different effects, even though used for different primary purposes. Either could destroy metastases. Both of the cases presented here did have x-ray therapy to which their eventual survival might be attributed.

Incidentally, there is one hazard of preoperative x-ray treatment that I have not found mentioned in the literature. At least it seems to be a hazard in Kentucky. In two of our cases, as soon as the mass disappeared from the abdomen the patient also disappeared into the Kentucky hills. I am no foe of preoperative x-ray therapy, but I am in agreement with the essayist that no long delaying period should be assigned to it. Are the known hazards of x-ray therapy after all sufficient to try to avoid its use? The most common danger is probably to young epiphyses. A young woman of my acquaintance traded a childhood sarcoma for a scoliosis. She wears braces and enjoys life tremendously. I have not asked her but it seems obvious she considers the bargain worth while. That deaths have occurred from x-ray treatment should not be forgotten, yet their number must be infinitely small beside the long list of deaths from the disease. I feel that I must continue to use a treatment that has some danger for a disease that is of *excessive* danger.

I have in the past succumbed, as Dr. Teasley has, to that discussion-ending question of the roentgenologist, "Doctor, what shall I shoot at? You say you saw nothing. I cannot spray the whole body!" I am no longer cowed, however, and I think that attitude of the roentgenologist should be resisted. He does not need a visible target. Metastasis is always microscopic before it is gross, and there is good reason in the known course of the disease to expect its appearance in the lymphatics or tissues in the area from which the tumor was removed. You can tell him where that area is.

In presenting beliefs that oppose the essayist's suggestions, I do so aware that none of us know the truth. I would add my plea to Dr. Teasley's for a central agency to accumulate the total experience with these tumors.

Dr. Carl Rusche, Los Angeles, Calif. It is a great honor and privilege to have the opportunity of participating in this fine and interesting program. I sincerely feel that Dr. Teasley has given us a fair and unbiased review of Wilm's tumor.

Undoubtedly you are aware of the existence of the confusion and disagreement concerning the management and treatment of Wilm's tumor in infancy and childhood. This exists not only among urologists but also among other members of the medical profession; that is, they may be pediatricians, internists, general practitioners, general surgeons, pediatric surgeons, and radiologists. This situation is particularly annoying and perplexing to those of us who are entrusted with the responsibility of teaching medical students and training urologic residents.

Today, I would like to emphasize the value of retrograde pyelographic studies on all children with an abdominal tumor. In our experience, the intravenous urogram has been unsatisfactory in a high percentage of cases. The diagnosis of Wilm's tumor is nearly always made in children under five years of age with an abdominal mass and immediate nephrectomy is advised. However, at the time of surgery, various anomalies of the urinary tract are discovered. It is well known that the most common abdominal mass in infancy and childhood is hydronephrosis. Neuroblastoma arising from the medulla of the adrenal presents a problem which can be solved only by exploration of the mass.

Much discussion in still indulged in regarding treatment of Wilm's tumor. At present, the majority of authors favor immediate surgical removal and postoperative radiation. These tumors are extremely radiosensitive and exhibit a marked reduction in the size of the abdominal mass after a few hundred roentgens of irradiation have been given (within 24-48 hours). I have always considered the procedure a distinct aid in confirming the diagnosis of Wilm's tumor, because when dealing with a clear-cell tumor, or a benign lesion, there will not be a change in the size of the mass. Again, the shrinking of the mass greatly facilitates its surgical removal and I question very strongly whether it actually jeopardizes the child's chance to recover. In my opinion, preoperative radiation for a period of 5-7 days, then transperitoneal nephrectomy to be followed by postoperative radiation is the treatment of choice.

The prognosis in these cases is shockingly poor. Recurrent growths are very rapid. It is my conjecture that if the patient lives for two years, the probability of recovery is good. However, there have been 5 cases in our series, who have died of the disease after three years. In a review of 71 cases collected from Los Angeles Children's Hospital and our private practice during the past 28 years, those treated with surgery, a few with preoperative and all with postoperative irradiation, have shown the following results: 42 died within one year; 15 died within the next year; 13 lived more than five years; 7 of 12 patients are alive over a period of 10 years. One is in good health after 26 years, has married and has 2 children, following pre- and postoperative irradiation at the age of three years. In this series, there were 4 cases of bilateral tumor and one infant with a tumor at birth.

Dr. Teasley (Closing). I appreciate very much the generous discussion on my presentation. The subject is controversial. It is believed that the study of a large survey from many urologists would be of value in determining the status of postoperative irradiation for Wilm's tumor. Review of the literature on this subject is discouraging in attempting to arrive at some definite conclusion because all reports are not complete in outlining postoperative care.

Oliver Wendell Holmes on Puerperal Fever

The practical point to be illustrated is the following: The disease known as puerperal fever is so far contagious as to be frequently carried from patient to patient by physicians and nurses. . . .

1. It is granted that all the forms of what is called puerperal fever may not be, and probably are not, equally contagious or infectious. . . .

2. I shall not enter into any dispute about the particular mode of infection, whether it be by the atmosphere the physician carries about him into the sick-chamber, or by the direct application of the virus to the absorbing surfaces with which his hand comes in contact. Many facts and opinions are in favor of each of these modes of transmission. But it is obvious that, in the majority of cases, it must be impossible to decide by which of these channels the disease is conveyed, from the nature of the intercourse between the physician and patient.

3. It is not pretended that the contagion of puerperal fever must always be followed by the disease. It is true of all contagious diseases that they frequently spare those who appear to be fully submitted to their influence. Even the vaccin virus, fresh from the subject, fails every day to produce its effect, though every precaution is taken to insure its action. This is still more remarkably the case with scarlet fever, and some other diseases.

4. It is granted that the disease may be produced and variously modified by many causes besides contagion, and more especially by epidemic and endemic influences. But this is not peculiar to the diseases in question. There is no doubt that smallpox is propagated to a great extent by contagion, yet it goes through the same period of periodical increase and diminuation which have been remarked in puerperal fever. . . .

5. I take it for granted that, if it can be shown that great numbers of lives have been and are sacrificed to ignorance or blindness on this point, no other error of which physicians or nurses may be occasionally suspected will be alleged in paliation of this; but that whenever and wherever they can be shown to carry disease and death instead of health and safety, the common instincts of humanity will silence every attempt to explain away their responsibility.

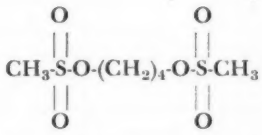
—From the *New England Quarterly Journal for Medicine and Surgery*, 1843.

Myleran in the Treatment of Chronic Myeloid Leukemia: Results of Treatment*

CHARLES L. SPURR, M.D., WILLIAM L. WILSON, M.D., and JAMES F. McDONALD, JR., M.D.,† *Houston, Tex.*

This drug has been introduced in recent years for the treatment of chronic myelogenous leukemia. It seems to be effective in inducing remissions of varying lengths of time.

THIS REPORT DEALS WITH OBSERVATIONS made over a two year period in the use of Myleran (1:4 dimethanesulphonyloxybutane) in the treatment of chronic myelocytic leukemia. This material, developed at the Royal Cancer Hospital, London, was first explored as an extension of studies on the aromatic analogues of the nitrogen mustards for use in tumor chemotherapy. Timmis and Haddow,[1] in studying a series of sulphonic acid compounds, found a substance with the structure indicated below,



which inhibited animal tumors, in particular the Walker rat carcinoma 256, and had a depressive influence on the myeloid series both in the rat and in man. Elson[2] compared the effects of Myleran with those of the x-ray and nitrogen mustard, and found that, unlike the latter two agents, Myleran did not depress lymphocyte formation in a dose which caused a 50 per cent or more decrease in the number of neutrophils. These findings encouraged investigation of the clinical usefulness of this material in the palliation of myeloid leukemia. Galton,[3] in 1953, reported the results of his studies with this material at the Royal Cancer Hospital. Petrakis[4] and others were the first to report on their experience in the use of this compound in this country. Wintrobe[5] and his co-workers have recently reported their results in 16 cases, and Galton,[6] in February 1955, added to his original report. All these studies have demonstrated the efficacy of this material in chronic granulocytic leukemia. The exact mode of action has not yet been elucidated, but the selective action of Myleran on myeloid cells within controlled therapeutic range is established; indeed, this is the basis of its value.

The present study undertakes a report of 11 cases treated with this agent on a maintenance basis rather than on the basis of a therapeutic course as described by most of the above workers.

Technic and Observations

Dose. Our Myleran therapy has been primarily designed as a maintenance program. Daily doses varied from 2 to 8 mg. The initial dose was usually 6 mg. per day. Rarely, it was increased to 8 mg. per day; our policy is now to reduce the dose when a decline in leukocyte count appears. The total dose given our patients varied from 244 to over 3,000 mg. The average daily dose over the entire treatment period was 3.2 mg. The usual maintenance dose is 2 mg. per day, although some patients require alternate daily doses of 2 and 4 mg.

Hematologic Observations. Blood studies included pretreatment bone marrow aspiration, erythrocyte count, hemoglobin, hematocrit, leukocyte count, differential count, and platelet count, the latter being carried out by the direct technic with Rees-Ecker fluid. At the onset of treatment blood counts were made three times a week but, when satisfactory remission was attained, studies were repeated every 2 to 3 weeks. The period of observation of these 11 cases has varied from

*Read before the Section on Medicine, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

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TABLE 1

CHEMOTHERAPY OF CHRONIC MYELOCYTIC LEUKEMIA WITH MYLERAN
PRIOR THERAPY, DURATION OF TREATMENT AND DOSAGE

Patient	*Prior Therapy*	*Adjunctive Therapy*	*Length of Observation*	*Length of Treatment with Myleran*	*Total Dose*	*Average Daily Dose**
1. S.S.	Purinethol 7600 mg.	None	6/6/53 to present	11/18/53 to present	3261 mg.	4.4 mg.
2. L.W.	None	Blood transfusions	12/9/53 - 3/4/55	12/14/53 - 3/4/55	244 mg.	3.1 mg.
3. A.R.	None	2 blood transfusions	2/17/54 to present	2/24/54 - 9/22/54 2/2/55 to present	1532 mg.	2.4 mg.
4. R.P.	None	None	9/8/55 to present	9/10/55 to present	266 mg.	3.6 mg.
5. J.T.	None	None	1/28/55 - 8/24/55	1/31/55 - 8/24/55	700 mg.	3.4 mg.
6. A.A.	None	None	12/3/54 to present	12/6/54 - 6/29/55 8/31/55 to present	1357 mg.	3.9 mg.
7. D.T.	None	None	3/16/54 to present	3/16/54 to present	1164 mg.	1.9 mg.
8. L.B.	TEM X-ray	None	11/12/53 to present	7/14/54 - 5/1/55 9/27/55 to present	552 mg.	1.1 mg.
9. C.L.	Transfusions	None	12/21/53 to present	12/24/53 - 2/20/55	888 mg.	2.9 mg.
10. P.G.	X-ray	Purinethol p22 Transfusions	9/15/53 - 8/22/55 Expired	5/22/54 - 3/23/55	1146 mg.	3.5 mg.
11. M.C.	None	None	1/12/55 to present	1/24/55 - 3/28/55	294 mg.	4.7 mg.

*Where treatment was interrupted and later resumed, the average daily dose was calculated on the number of days in the total period, including periods when treatment was temporarily withheld.

2 to 29 months, with an average observation period of 12 months.

Clinical Observations. Tables 1, 2, and 3 summarize some of the results obtained in 11 cases of chronic granulocytic leukemia thus treated.

A definite clinical and hematologic remission was seen in 10 of these cases. The other case, although showing no hematologic improvement, no longer requires transfusions as the patient did prior to Myleran therapy and is in clinical remission. Two of our 11 patients have died; the remaining 9 show a satisfactory status. In this group of 9, one patient (A.A.) had an excellent hematologic and clinical remission but stopped Myleran of his own volition for 2 months. A relapse ensued but he has again responded to this drug.

Our indications for therapy included leukocytosis, anemia, and splenomegaly. Four patients had received prior therapy, in the form of triethylene melamine, Purinethol, or x-ray; adjunctive therapy during the period of treatment with Myleran, however, was used in only one case (P.G.).

Therapy was discontinued by us in three

TABLE 2

CHEMOTHERAPY OF CHRONIC MYELOCYTIC LEUKEMIA WITH MYLERAN
CHANGES IN LEUKOCYTE AND HEMOGLOBIN LEVELS

Pt.	*W. B. C.*			*Hgb.*		
	At Initiation of Myleran Therapy	*After 3 Mos. of Therapy*	*Last Observation*	*At Initiation of Myleran Therapy*	*After 3 Mos. of Therapy*	*Last Observation*
1	182,000	34,750	16,400	14.9 Gm.	14.9 Gm.	14.3 Gm.
2	593,000	8,500*	320,000	8.9 Gm.	9.9 Gm.*	6.5 Gm.
3	371,000	30,250	30,800	9.2 Gm.	14.4 Gm.	13.9 Gm.
4	299,000	44,110*	14,500	8.1 Gm.	13.3 Gm.*	14.3 Gm.
5	409,500	50,000	30,600	9.4 Gm.	14.8 Gm.	15.6 Gm.
6	562,000	56,000	89,500**	6.0 Gm.	11.4 Gm.	11.2 Gm.**
7	800,000	7,700	6,300	9.0 Gm.	15.0 Gm.	15.8 Gm.
8	259,000	5,500†	11,500	9.0 Gm.	9.5 Gm.	13.5 Gm.
9	6,850	12,600	38,000‡	10.1 Gm.	10.3 Gm.	10.0 Gm.
10	82,500	8,050	99,500	12.6 Gm.	14.5 Gm.	5.3 Gm.
11	112,000	3,700	7,100	9.9 Gm.	10.4 Gm.	11.9 Gm.
Average	334,200	23,740	60,380	9.7 Gm.	12.6 Gm.	12.0 Gm.

*These observations were made at 6 weeks. Total duration of observation was a little less than 3 months.
**This patient discontinued Myleran of his own volition for a 2-month period and his white count went from 18,100 to 268,000. Myleran therapy was reinstituted and he is again responding.
†Observation at 5 weeks—patient temporarily out of observation for a period thereafter.
‡Myleran therapy discontinued by us in February. Satisfactory clinical remission has been maintained since.

cases. Two patients developed leukopenia and thrombocytopenia (M.C., L.B.) and, in the third (C.L.), the drug was withdrawn because of serious intercurrent disease. These three cases have remained under observation and are in good clinical remission.

Hematologic Observations.

Leukocytes. The leukocyte and hemoglobin levels are summarized in table 2. For simplicity of presentation we show these values at initial observation, at 3 months after initiation of therapy with Myleran, and at our last observation.

Level of white count, immaturity of white cells, level of hemoglobin, spleen size, and general symptomatology have all been used as indices of the general progress of therapy.

Our experience is that initially there is a very sharp drop in white count. We found that in almost all cases the white count began to drop appreciably within two weeks, although in one case (No. 5, J. T.) there was no drop until 25 days. The maximal drop occurred in varying periods of time, in one case (M.C.) occurring in about 2 weeks, but in most cases occurring in a longer period of time, up to 7 months. Table 2 shows the significant fall generally occurring in three months. The average white count at the beginning of therapy was found to be 334,200 and the average level of white count after three months of therapy was 23,740. The average white count at the last observation of these patients was 60,380. This figure is considerably influenced by the two patients who relapsed and died. It is stated in the literature[5] that the time taken for a given leukocyte count to return to normal is proportional to the logarithm of the initial count and is related to the daily dose of Myleran. Galton[6] has stated that one may expect the white count in Myleran therapy to halve each month.

Hemoglobin. It may be that the hemoglobin level is a more reliable guide than is the leukocyte count in estimating the results of therapy. Our experience has been that, as a rule, there is a rise in hemoglobin level within 2 to 4 weeks. In our 11 cases, the average hemoglobin level at the start of therapy was 9.7 Gm., the average rise in three months' time was 2.85 Gm. Excluding patient No. 11, who relapsed and died, and whose hemoglobin level declined markedly prior to his death, the average rise in three months' time was 2.85 Gm. Excluding the patient of case No. 11 on the same bases, who relapsed and died, the average rise in hemoglobin in all cases from the beginning of therapy to last

TABLE 3

CHEMOTHERAPY OF CHRONIC MYELOCYTIC LEUKEMIA WITH MYLERAN
THROMBOCYTE LEVEL, SPLEEN SIZE AND CURRENT CLINICAL STATUS

Pt.	Platelets		Spleen Size		Period of Remission with Myleran Therapy	Current Status
	At Start of Myleran	*Last Observation*	*At Start of Myleran*	*Last Observation*		
1	366,000	684,000	2 fb below costal margin	Not palpable	24 months	Good
2	30,000	80,000	Below umbilicus	Below umbilicus	6 weeks	Expired
3	300,000	550,000	3 fb below umbilicus	At costal margin	22 months	Good
4	280,000	284,000	Below umbilicus	Not palpable	2 months	Good
5	496,000	454,000	4 fb below umbilicus	4 fb below costal margin	11months	Good
6	376,000	1,072,000	4 fb below umbilicus	2 fb below umbilicus	7 months*	Good
7	200,000	69,980	1 fb below costal margin	At costal margin	21 months	Good
8			2 fb below costal margin	Not palpable	16 months†	Good
9	60,000	48,000	2 fb below costal margin	At costal margin	21 months	Good
10	200,000	12,000	At iliac crest	At iliac crest	9 months	Expired
11		140,000	Below umbilicus	At costal margin	10 months	Good

*Patient had a relapse when he discontinued Myleran therapy of his own volition. He is now in remission again.
†This patient had a relapse when he discontinued Myleran therapy of his own volition and like patient 6, is now again in remission with resumption of therapy.

observation was 3.25 Gm. The rise in hemoglobin varied from 0 to 6.2 Gm. A striking feature of the hemoglobin rise observed in these cases was that it occurred without transfusion or other adjunctive therapy.

Platelet Counts. The action of Myleran on platelets is of much interest. Four patients (D.T., A.R., M.C., P.G.) developed thrombocytopenia during therapy, though none of these developed purpura or other hemorrhagic difficulties. Three remitted upon interruption of therapy and, in one (P.G.), thrombocytopenia appeared to be a terminal event, not necessarily resulting from Myleran therapy. Two patients (L.W., C.L.) had low platelet counts at the initiation of therapy and without constant significant change during therapy.

In general, it has been our experience that serious thrombocytopenia as a result of therapy is an uncommon occurrence on the dosage schedule which has been used. Indeed, in several cases, for instance the first, third, and sixth cases shown in the table, a thrombocytosis developed, whether as the result of Myleran therapy or not one cannot say since thrombocytosis is not an uncommon occurrence in the course of chronic myelogenous leukemia. In no cases were difficulties encountered as a consequence of thrombocytosis.

Splenomegaly. The size of the spleen is also valuable in judging response to treatment. It decreased quite considerably in 9 of the 11 patients treated. The rapidity of onset of change in splenic size is perhaps not as susceptible to precise estimation as are other determinations, but tabulation of our results indicates that a decrease in the size of the spleen commonly occurred within a month.

Subjective Clinical Status. In all patients in whom a remission was obtained, there was a definite improvement in the general sense of well being, concomitant with a decrease in symptomatology.

The only untoward effects we encountered with the use of this agent were the episodes of thrombocytopenia without purpura previously mentioned, and one incident of brownish pigmentation of the skin occurring in a female patient (M.C.). We concur in the general experience that this agent is remarkable in its freedom from all action on any system other than the hemopoietic.

Case Presentations

We present two cases exemplifying different aspects of Myleran therapy.

Case 3. Figure 1 shows some of the features noted in following case A.R. over a period of 22 months.

The patient was first seen February 17, 1953, with a 3 year history of gradual weight loss of about 40 pounds, undue fatigability for 2 years, and a progressively enlarging mass in the left upper quadrant. Lymphadenopathy, splenomegaly and hepatomegaly were noted on initial physical examination and a white blood count of 371,000 was found with a hemoglobin of 9.2 Gm. and a platelet count of 300,000. The spleen was palpable below the level of the umbilicus. Bone marrow aspiration was performed which confirmed the clinical impression of chronic myelocytic leukemia.

The patient was started on Myleran, 6 mg. per day and, two months later, in April, his white count had fallen to 30,000. Although it is not represented graphically, there was marked fall in the proportion of immature white cells in the peripheral blood. The hemoglobin at that time had risen to 14 Gm., the platelet count was stable and the size of the spleen was decreasing. At this time the patient was admitted to the hospital for a herniorrhaphy and Myleran was temporarily discontinued. Thereafter, in May, he was again started on 4 mg. of Myleran and it may be seen that the splenic size decreased progressively. The white count had come down to 10,000 by June, 1954, the hemoglobin was at 13 Gm. The patient was continued on 2 mg. Myleran per day.

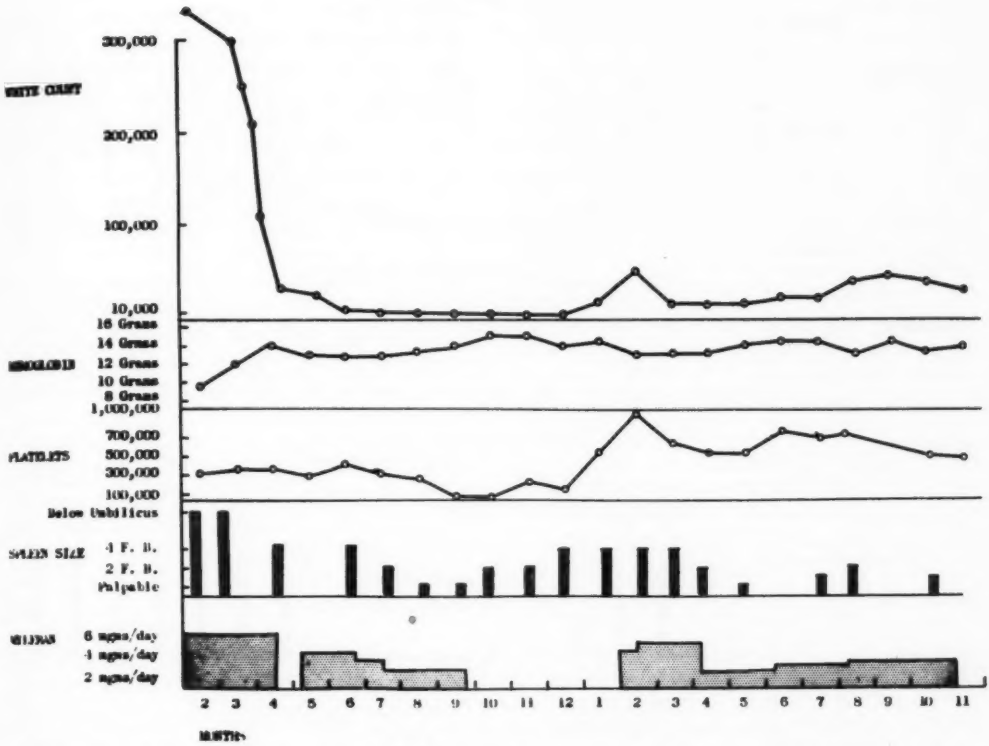
A second sternal marrow aspiration done in August, 1954, showed increased myeloid activity but it was thought that it would be difficult to make a diagnosis of myeloid leukemia on the basis of the slide. In September, 1954, his platelet count declined to slightly under 100,000, and for this reason Myleran was discontinued. Thereupon, the platelet count rose. Myleran was not given for 5 months. There was a slight fall in hemoglobin, some rise in white count by February, 1955, and a definite increase in the size of the spleen. Myleran was started again and his white count fell, his hemoglobin resumed its former level, and the size of the spleen again declined. Since that time, the patient has been maintained on a dose of Myleran varying between 2 and 3 mg. per day.

In November, 1955, he was completely asymptomatic; the peripheral blood count showed 30,000 white cells with a hemoglobin level of 14 Gm., a platelet count of 550,000, and a spleen which is just palpable at the costal margin. He is, at present, actively employed.

Case 11. Figure 2 illustrates the course of a patient who did well initially, but subsequently relapsed and died. The figure deals only with the patient's course after he was put on Myleran.

He was first seen on October 6, 1953, with a history of loss of appetite and progressive weight loss dating from 1951. He had himself noted a mass in his left upper quadrant. A diagnosis of chronic myelocytic leukemia had been made just prior to his entry to

FIG. 1



Case 3. This reflects control of chronic myeloid leukemia over a 22 month period by the use of a maintenance dose of Myleran.

this hospital and he had been treated with x-ray and transfusions.

The spleen on entry was found palpable at the iliac crest. His white count on entry was 21,900, hemoglobin, 10.1 Gm. and, platelet count, 200,000. Sternal marrow aspiration was done and the diagnosis of chronic myelocytic leukemia was confirmed.

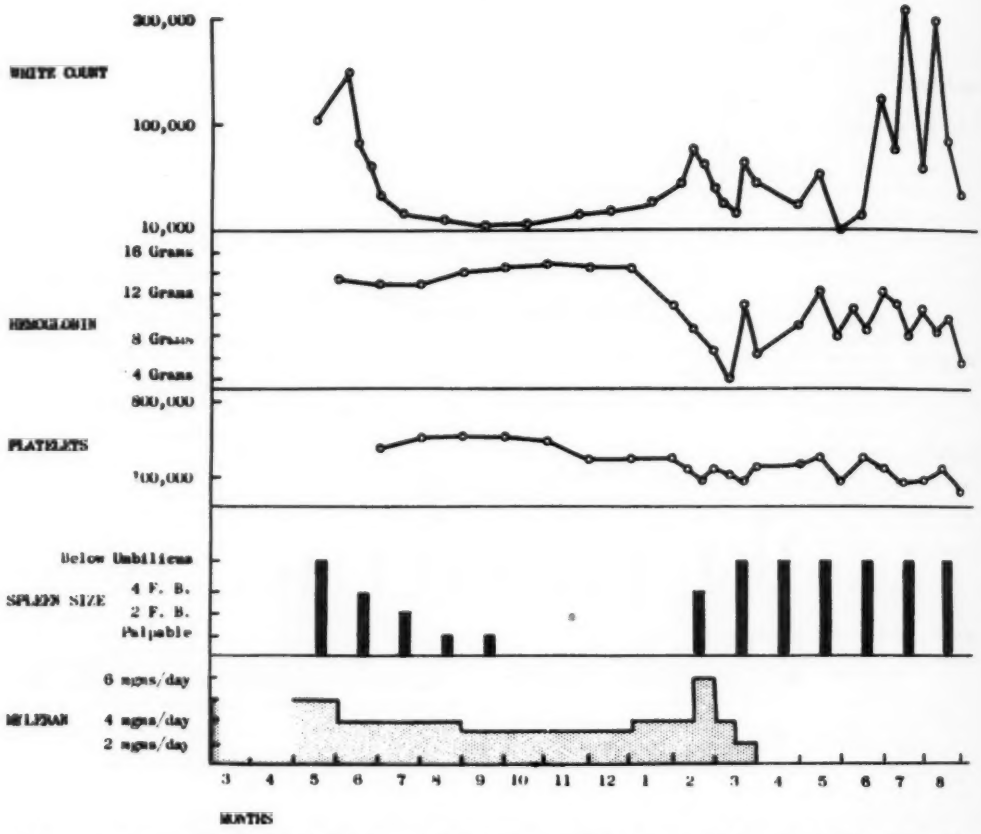
X-ray therapy given just prior to entry to the hospital induced a remission which lasted from September, 1953, until the spring of 1954. In May, 1954, it was noted that the size of his spleen had increased, the leukocyte count had risen to 97,000 and the hemoglobin had declined and, therefore, he was started on therapy with Myleran. He was originally treated with 6 mg. per day and his white count, which reached a high of 150,000, declined sharply, and 2 months after initiation of therapy was 14,000. At this time, his hemoglobin and platelet count were unchanged and his spleen size was decreased. By August, 1954, his white count was 10,000, his hemoglobin level was just under 14 Gm., his platelet count was over 400,000 and his spleen size had decreased markedly. The dose of Myleran was decreased progressively and, in October, his spleen was not palpable, and his hematologic findings were satisfactory. At this time, he was maintained on 3 mg. of Myleran per day.

In January, 1955, his white count began rising and numerous myelocytes were seen in the peripheral smear. His hemoglobin began falling, his spleen became larger, and a sharp increase in the splenic size became evident. The dose of Myleran was increased and there ensued a fall in white count, but with a continued decline in hemoglobin level. Thereupon, Myleran was discontinued and the patient was treated with Purinethol and with blood transfusions. Purinethol induced a marked leukopenia which prompted withdrawal of the drug. Severe anemia, requiring frequent transfusions was present.

The patient's further course may be summarized briefly by saying that he declined progressively, the size of the spleen increased, anemia became more marked, and required increasing transfusions. Radioactive phosphorus was given without improvement. Terminally his platelet count dropped to very low levels, although he never showed any bleeding tendency.

It has been stated that resistance to Myleran may develop. It is possible that this second case exemplifies such resistance. In February, 1955, when this patient went into what was eventually seen to be his final relapse, his

FIG. 2



Case 11. This shows a good case of chronic response to maintenance therapy but relapse from control after 11 months.

hemoglobin level, despite continued Myleran therapy, dropped sharply.

We may now ask how Myleran therapy compares with other forms of treatment, specifically with radioactive phosphorus or with x-ray therapy which, hitherto, has been the most successful treatment for myelocytic leukemia. This question cannot be answered with certainty until such time as sufficient cases have been treated with Myleran alone to permit statistical analysis. Our own clinical impression has been most favorable. We concur, likewise, in the opinion of others that Myleran is superior to any other chemotherapeutic agent available.

As to the pros and cons of interrupted versus maintenance therapy, the reader is referred to the paper by Galton[6] in which a discussion of this problem is presented. Our principal experience has been with the maintenance type of treatment which we favor.

6-Mercaptopurine

Another chemotherapeutic agent, 6-mercaptopurine, has, like Myleran, been used in the therapy of chronic granulocytic leukemia, and we should, therefore, like to comment briefly on it.

This material, with the proprietary name of Purinethol, developed by Hitchings and associates,[7] is unique in that it is the first successful therapeutic agent synthesized by biochemical design rather than empirically (Fig. 3). It is a purine antagonist and interferes with the biosynthesis of nucleic acids.[7]

Numerous clinical trials have established

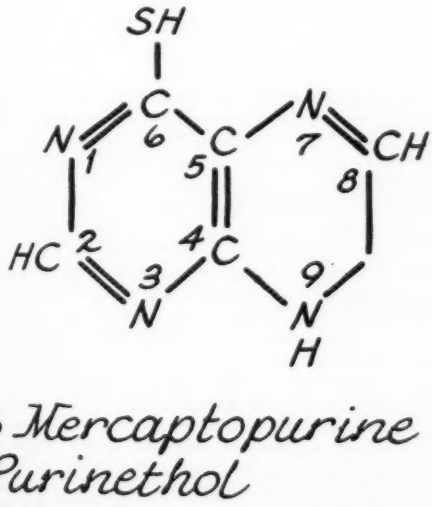
its usefulness in the control of the acute leukemias and in chronic myelocytic leukemia. It has been found to be without value in solid tumors and in chronic lymphocytic leukemia.[7] The most common dose is 2.5 mg. per Kg. of body weight per day, although higher doses have been used in those cases not responding to the initial dose.

Its principal toxic effect is hematologic depression, although oral lesions and gastrointestinal lesions occur occasionally.[7,8] Nevertheless, the relative lack of toxicity of this agent, as compared to the antifolic group, has been one of its advantages.[9]

Probably the chief indication for its use is acute leukemia. It has been more effective in children than in adults.[10] A number of instances have been recorded[9,11] in which a remission was induced with Purinethol in subjects who had previously been resistant to the other agents used in the treatment of acute leukemia, folic acid antagonists, and steroids.

In acute leukemia complete, as contrasted with partial remissions, have been associated with some suppression of hemopoiesis which is followed by regeneration after withdrawal of the drug.[12] Because of its relatively slow onset of action it is probably not the agent of choice in the more rapidly progressive acute leukemias.[9] Here the folic acid antagonists are to be preferred. The combination of this agent with other drugs or with cortisone has been advocated and is perhaps best applied to adults.[10] This substance has been successful in inducing a remission in a number of early cases of chronic myelocytic leukemia. It has been stated to have considerable value in the terminal phases of chronic granulocytic leukemia, indeed, to be the agent of choice in this situation.[13]

FIG. 3



Structural formula of 6-mercaptopurine, Purinethol.

TABLE 4

AGENTS USED IN CHRONIC MYELOID LEUKEMIA
The first three seem to be the most effective

Myleran
Radioactive Phosphorus
X-ray
6-Mercaptopurine
Urethane
Nitrogen mustard
Triethylene melamine

Although no systematic comparison has been made between Myleran and Purinethol in the treatment of chronic myelocytic leukemia, certainly the results obtained with Purinethol as published in the literature are inferior to those we have become accustomed to witnessing with Myleran. In this respect our experience conforms with that of others.

Table 4 summarizes the agents useful in the treatment of chronic myeloid leukemia. Those shown in italics are considered to be of paramount importance. The others are capable of inducing remissions, have special indications, and may be used in certain instances where the primary agents have failed.

Summary

Certain general statements about the use of Myleran therapy are warranted, although no final conclusions can yet be drawn.

It is undoubtedly an effective agent for induction and maintenance of remissions in chronic myelocytic leukemia. None of our cases failed to show a response. This drug appears to be characterized by a remarkable specificity of action, an advantage not shared by other modes of therapy of this disorder now in use.

Is there any danger connected with the use of this agent? Careful hematologic observation is necessary; with this proviso, we believe the treatment to be safe. We do not believe thrombocytopenia an undue hazard in carefully observed cases on the dosage schedule

here used, although, with the higher doses originally used by British workers, and since abandoned, it may undoubtedly present difficulties.

Transformation to the acute myeloblastic stage did not occur in our observation, although it has been reported by Galton,[3,6] and by Levin and his co-workers.[14] In the case just presented (P.G.), a bone marrow examination after final relapse showed a predominance of myelocytes and promyelocytes.

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Discussion (Abstract)

Dr. David C. Miesch, Galveston, Tex. I feel honored to have been asked to discuss this paper covering the authors' clinical experience with Myleran and Purinethol in the management of myeloproliferative disorders. I will limit most of my remarks to Myleran and its use in the treatment of chronic myeloid leukemia. In my opinion they have covered a timely subject quite well. I say timely because, although Myleran has been in wide use since mid-1953 (and earlier in Britain where it originated), it is only about now that sufficient time has elapsed and enough data collected to permit an estimation of its true place in the management of chronic myelocytic leukemia.

At the present time it seems that all observers are having similar results with this drug, and these results are all quite favorable. The data in Dr. Wintrobe's recently published account of 14 cases are comparable in most respects to those of Drs. Spurr, Wilson and McDonald. Our experience at the John Sealy Hospital, of the University of Texas Medical Branch in Galveston, is again quite similar. Up to this time we have treated 13 patients with chronic myelocytic leukemia with Myleran. The clinical and hematologic results have been so rewarding that since mid-1953 we have only rarely reverted to the therapeutic tools which were at that time our mainstays, namely radioactive phosphorus and spray irradiation. At least it seems to us that the selectivity of action on the myeloid elements by Myleran, the lack of significant side effects, and the relative ease and safety with which it can be administered to patients even on an out-patient basis (when adequate laboratory facilities are available and utilized) all point to the fact that Myleran is now without any doubt the treatment of choice in chronic myelocytic leukemia. However whether it is actually superior to the older method of treatment such as x-ray is quite difficult to say.

There are several observations which we have made during our use of this drug which have intrigued us, and might be of interest to the group in general.

First, as Dr. McDonald has mentioned, the literature mentions a few cases of individuals with chronic myelocytic leukemia who, during the course of treatment with Myleran, developed a rather rapid transformation of their hematologic picture to that of an acute myeloblastic leukemia. In our series of 13 cases there were two individuals in whom this has developed. There was a rapid acceleration of their downhill course following the administration of Myleran, and they succumbed within several months time. The hazards of drawing any sweeping conclusions on the basis of only two cases is obvious, particularly as it has been observed that in an occasional case of chronic myelocytic leukemia this course may be pursued unrelated to therapy and apparently as a part of the natural course. Nevertheless, two cases out of 13 does seem somewhat excessive, and I thought it merited mention at least.

Another observation we have made may be of general interest. Three patients of our cases during the administration of an ordinary course of Myleran developed a marked hypoplasia of the bone marrow and pancytopenia of the peripheral blood. The Myleran was of course discontinued and the hypoplasia gradually disappeared over about a month's time. The interesting thing is that of these three patients one is still in an excellent remission without any subsequent treatment some 15 months later with a bone marrow and peripheral blood which might be taken for normal if the preceding circumstances were not known. The second patient is still in excellent remission without treatment 5 months after the hypoplasia. The third patient has relapsed. The excellence and longevity of the remissions in the first two patients makes one almost wonder whether the severe hypoplastic episode which they experienced might not have been beneficial in the long run. This type of observation has been made previously in the instance of treatment

of acute lymphatic leukemias with Purinethol and Amethopterin. It almost makes one wonder whether he did not come close to eradicating the leukemic process as a result of the hypoplasia; however, this approaches the philosophic realm.

In regard to our experiences concerning the effect of Myleran on platelets, with the exception of the above cases of pancytopenia and hypoplasia, we have only twice noted thrombocytopenia which could be ascribed to Myleran, and these were mild and clinically not significant. In agreement with Dr. Spurr we likewise have noted thrombocytosis following the institution of Myleran therapy; however, in our experience this thrombocytosis has apparently been seen less often and has been less striking.

Along with Dr. Spurr we have preferred maintenance therapy with Myleran in contrast to the intermittent therapy employed by Wintrobe and others. All of our cases except those with hypoplasia have been on maintenance therapy from the start, and we have, generally speaking, experienced little difficulty in arriving at the maintenance dose for an individual patient.

I have no further comments to make except that this is indeed a valuable addition to the therapeutic armamentarium for the treatment of chronic myelocytic leukemia.

Dr. R. W. Rundles, Durham, N. C. There is very little that one can add to this good paper on the use of Myleran. Everyone is well satisfied with its immediate effect in chronic granulocytic leukemia. Unfortunately, it does not appear to materially postpone or prevent the development of the acute phase or terminal exacerbation of the disease.

It was good to hear the authors recommend maintenance therapy. Continuous control of the disease, rather than the production of a series of remissions followed by relapses, is a logical and practical strategy for the preservation of a maximal span of health.

The depressant effect of Myleran on platelet production is ordinarily not a hazard in therapy. In some individuals the excessive proliferation of platelets, productive of vascular complications, can be controlled by this chemical. The effect of Myleran in polycythemia vera, myeloma, and in lymphocytic leukemias deserves further study.

The term "resistance" in leukemia to a therapeutic agent is sometimes used with an incorrect inference. Granulocytic leukemia tends to become progressively worse with the passage of time. When one agent becomes ineffective, all others with a comparable action, —x-ray, P^{32}, nitrogen mustard, TEM, urethane,—also fail. The major problem in myelogenous leukemias is to develop agents not only immediately effective, but which will prevent the progressive increase in severity of the basic disease.

HOTEL RESERVATION APPLICATION FORM

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Sclerotic Polycystic Ovary Syndrome*

CLARENCE D. DAVIS, M.D., *Columbia, Mo.*, JOHN R. ASHE, M.D., *Charlotte, N. C.*, and JAMES AUSTIN, M.D.,† *Durham, N. C.*

The authors bring out the need for visualizing the ovaries before doing a laparotomy for the syndrome suspected to be due to sclerotic polycystic ovaries.

THE SYNDROME OF THE SCLEROTIC POLYCYSTIC OVARY (Stein-Leventhal) is characterized by an abnormal estrogen metabolism, which leads to alterations in periodic uterine bleeding and anovulation. This may result in true primary or secondary amenorrhea, infrequent uterine bleeding, or even too frequent and excessive uterine bleeding. Until recently there has been a tendency to limit this syndrome to varying degrees of infrequent bleeding. However, it is now clear that these sclerotic polycystic ovaries of the Stein-Leventhal type can be associated with any type of menstrual pattern.[1] DuToit[2] has even reported progestational endometrium. Sterility is an obvious sequence to anovulation. Hirsutism and moderate obesity is associated with the syndrome in approximately 50 per cent of the instances. Hypoplasia of the breasts is sometimes found, but none of these seem to be important criteria.

Pathologic Findings

The size of the ovary is apparently not of primary importance, as in more than one instance in our series, the ovary was not appreciably increased in size. The configuration, however, seems to be of importance since these ovaries tend to maintain the normal relationships as regards shape. That is, they rarely become globoid. A point that has not been emphasized sufficiently seems to be, that these ovaries are sometimes relatively insensitive to pain. I know of no explanation of this. On visualization the ovary has a typical pale smooth appearance, with minute (usually 0.5 centimeter or less) cysts being dotted just under the white thickened capsule, with a concentration of the cysts usually distal to the hilus. There have been authentic cases of this type of ovary also harboring corpora albicans as well as relatively recent corpora lutea. This, however, is the exception. The process is almost always bilateral. If the process is unilateral it is probably not, strictly speaking, the type of ovary we are discussing. It is difficult to tell whether these minute cysts are under considerable pressure or not. As one cuts through the thickened ovarian capsule, they tend to squirt as when eating a grapefruit, but this may well be due more to the difficulty of cutting through the capsule than intrinsic pressure in the cysts themselves.

Clinical Picture

It is important to keep this syndrome in the back of one's mind when one is dealing with what appears to be functional uterine bleeding. These patients are not of the hypogonadal type, although some observers have reported the syndrome to be associated with primary amenorrhea. Characteristically, menarche occurs at the usual time and periods are relatively normal for a few years; then they become progressively infrequent and scant. The patients usually show the normal feminine characteristics. If one accepts the definition of secondary amenorrhea as a nonappearance of bleeding for a year or longer, many more of these patients would be in the infrequent bleeding group rather than the secondary amenorrhea group. In general, in any treatment of any degree of delayed bleeding, there seems to be a positive correlation between the duration of the complaint and success of treatment. The shorter the duration the higher the percentage of reversion to a normal cycle. This does not appear to be characteristic when one is dealing with the sclerotic polycystic ovarian syndrome.

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Etiology

The etiology of the syndrome is not understood. Some consider it to be primarily in the ovaries,[3] others to be pituitary[4] in origin. The hormonal studies that have been reported to date indicate that the follicle stimulating hormone (FSH) levels are usually within normal limits.[4] The 17-ketosteroids are normal or slightly elevated, the estrogen levels are normal or relatively constant, and the pregnandiol levels are normal. However, it seems until such time as hormonal assays are more specific that definitive discussion of the etiology of this syndrome is in a realm of "arm-chair" speculation.

It is most surprising that the ovarian changes do not recur after wedge resection, and until the etiology is understood the explanation of this will remain wanting. There is also no adequate explanation of why such a procedure may benefit the patient or alter the syndrome. So far as we know we have the only recorded instance of apparent recurrence. Payne[5] reports return of cyclic menses in one proven instance following roentgen-ray therapy to the ovaries. Buxton[1] recently described an instance of this syndrome which was substantiated by culdoscopy but a wedging operation was refused. Some months later the woman became cyclic spontaneously. All these facts seem to make a clear-cut understanding of the cause even more difficult.

Diagnosis

One does not need any fancy hormonal assays to establish the diagnosis or to rule out other confusing situations. We have had little experience with the x-ray visualization of these ovaries, and while such procedures may be helpful it does not appear to us that they are conclusive enough and, with proper selection of cases, are not strictly necessary. The obvious argument for x-ray visualization of the ovaries is that it may aid in the proper selection of patients who deserve actual visualization of the ovaries. If the technics, as described by Stein[6] and others[7] are scrupuously followed they surely are of ancillary value. If there is a reasonable possibility of the syndrome being present, one is surely justified in doing one of the following procedures: pneumoperitoneum, gynecography, culdoscopy or posterior culpotomy. If the clinical evidence of excessive androgen production is striking, it may be that a preliminary trial with the response to cortisone might be used.[8] If the patient responds to this treatment one is obviously dealing with adrenocortical hyperplasia and not polycystic ovaries. However, in our experience this particular diagnostic dilemma is not common.

Clinical Study

Despite the fact that the syndrome was originally described by Stein in 1935,[9] it was not until 1950 that we became sufficiently impressed to start looking for patients with this syndrome. Herein, we think, lies a moral. Since 1950 we have seen 16* such patients in which the diagnosis was proved at operation. This must mean that the syndrome is much more common than is generally accepted, and that if one is looking for it, it can be diagnosed correctly preoperatively and be substantiated at operation far more frequently than is current practice.

General. The ages of these 16 patients ranged from 19 to 30 years. All were normally feminine. Most had had previous thyroid therapy but none had evidence of true hypothyroidism.

Infrequent scant bleeding. There were 11 patients in this group. Nine of these had wedge operations, and 6 of 8 had cyclic bleeding begin relatively promptly (2 to 6 weeks) postoperatively. Many of these menses were presumedly ovulatory as determined by endometrial biopsy, and basal body temperature. One patient did not have follow-up examination. Most of these patients had had previous steroid therapy with resultant withdrawal bleeding.

Excessive bleeding. There were 5 patients in this group, one had infrequent bleeding, two had more or less continuous bleeding, and two cyclic bleeding. Four of these 5 had had considerable previous steroid therapy without any lasting benefit. All 5 had cyclic bleeding after wedge resection, and most of the cycles were apparently ovulatory.

Anovulation. This was established by one and frequently two or more endometrial biopsies or uterine curettages in 12 patients. Three of these 12 also had uniphasic basal body

* Two patients are included through the courtesy of Dr. William See, Columbia, Mo. All others were seen at Duke Hospital.

temperature curves. One other patient had this type of curve. Proof of anovulation was not established in three patients.

Sterility. Three patients were primarily interested in infertility and one of these became pregnant following ovarian wedging. Two others of the infrequently bleeding group became pregnant but one aborted at two months. All three initial pregnancies occurred within 6 months of operation. One patient had had 2 pregnancies, the first terminating in 7 months neonatal death and the other successfully at term. None of the excessively bleeding group attained pregnancy.

Hirsutism. Five were slightly hirsute, the chin being the only common location. Three of these were in the infrequently bleeding group and two in the excessively bleeding group.

Obesity. Only two patients were obese and both were infrequent bleeders. Neither were improved either as regards their irregularity or their obesity by wedge resection.

Hormone levels. The 24 hour urinary 17-ketosteroid levels in the 7 patients studied (5 infrequent and 2 excessive bleeders) were within normal limits. The 24 hour urinary gonadotropin output was within normal limits in 6 (5 infrequently and one excessively bleeding) patients. One patient had levels two times normal. The technics used have been previously published.[10]

Cytology. Eleven of the patients had vaginal cytology studies. Five were reported as having a high percentage of navicular cells. This type of smear[11] seems to indicate a disturbance in estrogen metabolism but no decrease in cornifying agent. In one instance, at least, the diagnosis of sclerotic polycystic ovaries was suspected on the basis of the above finding.

Pelvic examination. In the infrequently bleeding group, 3 were thought to have ovaries of normal size, 2 unilateral enlargement and 5 symmetrical bilateral enlargement. None of these ovaries was thought to be over 2 to 3 times normal size. One patient in the infrequent group had one ovary that was 8 to 10 centimeters in size, and globoid, while the other ovary was only slightly enlarged. In the excessively bleeding group, 4 had unilateral and one bilateral symmetrical enlargement (2 to 3 times normal size).

Diagnosis. The diagnosis of sclerotic polycystic ovary syndrome was confirmed by wedge resection in 14 of our 16 patients. In two patients the diagnosis was established by culdoscopy only. Culdoscopy or visualization by posterior culpotomy was carried out in 13 patients. Three patients had a laparotomy without previous visualization of the ovaries. No unnecessary laparotomies were carried out because of this suspected diagnosis. Only one patient, who was subjected to culdoscopy to establish this diagnosis, failed to have the syndrome.

Operation. The wedge operation was done according to the principles of Stein. In one instance only was this done vaginally. The procedure was carried out bilaterally on both ovaries of all 14 patients. The only exception was the globoid ovary. Enough ovarian tissue was destroyed in the resection of this large cyst that it was thought simple rupture of the remaining minute subcapsular cysts was sufficient.

Pathology. All 14 patients who were subjected to the wedging operation showed characteristic microscopic changes in both ovaries excluding the above exception. One ovary had evidence of a hyalinized portion of an old corpus luteum. A small dermoid cyst in one ovary and two recent corpora lutea in the other ovary were found in another patient.

Complications. There were two major complications. One patient, who had the wedge resection performed vaginally had a large pelvic hematoma which necessitated laparotomy and resection of a tube and ovary two weeks after wedging. This patient, however, has continued to be cyclic in bleeding. Another patient had a unilateral pelvic hematoma which slowly subsided over a period of months.

Recurrence. One patient with excessive infrequent bleeding had an ovarian wedging operation which was promptly followed by pregnancy. This ended in a two months abortion and was succeeded by 14 months amenorrhea. Another laparotomy revealed a typical but unilateral sclerotic polycystic ovary and this was wedged again. The other ovary did not appear characteristic and was not wedged. The pathologist considered the specimen submitted to be typical of this syndrome. The patient was cyclic for 8 months following the

second operation and then was lost to follow-up study.

Prolonged follow-up. Nine of the 14 patients operated upon have been followed for over a year. In the infrequently bleeding group so far as we know only one has become acyclic (no bleeding for 3 months and not pregnant). This began 18 months postoperatively. The two infrequent bleeders who failed to respond initially have bleeding episodes three to four times a year as they had preoperatively.

In the excessively bleeding group, two were followed for less than 6 months. Two became amenorrheic 8 months and 4 years after operation. One remained cyclic for two and a half years and then had no further follow-up. So far as we know, none reverted to excessive bleeding.

Discussion

Our experience with this syndrome has led us to an index of suspicion in any instance of functional uterine bleeding. We have no way of knowing how many times we have missed the diagnosis. Only one unnecessary culdoscopy was done. One is rarely justified in doing a laparotomy for this condition without prior visualization of the ovaries.

The timing of this operation seems to be of importance, for reversion to amenorrhea may be much more common than we have been led to believe. Furthermore, most pregnancies seem to occur shortly after the operation. This means the state of the tubes should be evaluated and the seminal situation assayed preoperatively if sterility is a problem. If the patient is single or wishes to postpone pregnancy one should probably delay the operation. As pointed out previously the duration of symptoms does not seem to alter the success of the operation in properly selected patients.

The excessive bleeder with this type of polycystic ovary seems to respond very promptly to wedging by reversion to normal cyclic bleeding. However, in two of three patients whose course was followed for over 6 months amenorrhea finally ensued. From a strictly practical point of view one is probably better off with an amenorrheic patient than with an anovulatory one who is bleeding excessively. During the period of normal (ovulatory) bleeding which follows wedging, a chance for conception is present. None of our 5 patients conceived but others have reported pregnancies in this group.

Over 200 patients with this syndrome have been reported in the past two decades. There is no doubt that several times that number have been operated on. It is impossible to guess the countless numbers that have remained unrecognized and hence most likely are still sterile and have either infrequent or excessive bleeding. It is only by careful analysis of the individual situation and a greater willingness to visualize ovaries via the culdoscope, posterior culpotomy, or gynecography that this group can be reduced. Here is one type of functional uterine bleeding that stands a reasonable chance of cure, that is, a return of cyclic ovulatory bleeding.

Summary

1. Sixteen patients with bilateral sclerotic polycystic (Stein-Leventhal) ovaries are reported; 14 of these were diagnosed by wedge resection and two by culdoscopic visualization only.

2. Eleven had infrequent scant anovulatory cycles and five had excessive anovulatory ones. Following wedge resection six of eight of the infrequent bleeders changed to more or less cyclic bleeding, much of which was ovulatory. One of these reverted to amenorrhea 18 months postoperatively.

3. Five patients had excessive anovulatory bleeding. All five were cyclic postoperatively. One became amenorrheic four years later and another eight months after operation.

4. Only three of our patients became pregnant following the operation. One aborted at two months, one carried to term initially, and the third, had a seven months neonatal stillbirth which was followed by a successful term birth.

5. Obesity, hirsutism and hypoplasia of the breasts are not important factors in establishing this diagnosis.

6. Hormonal studies are only of ancillary help. Elevated urinary 17-ketosteroids will exclude the sclerotic polycystic ovary syndrome.

7. The diagnosis should be confirmed by visualization of the ovaries by posterior culpotomy, culdoscopy, or gynecography.

8. Wedge resection of the ovaries is not without immediate postoperative complica-

tions. Considerable caution should be taken in carefully suturing the ovaries. The operation carries a potential danger if carried out by the vaginal route.

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Discussion (Abstract)

Dr. Phil C. Schreier, Memphis, Tenn. My experience with the syndrome discussed by Dr. Davis is very limited. Like him, I have always been apprehensive about using this diagnosis as an indication for pelvic surgery for fear that less drastic measures may have been adequate. When subjected to studies and examinations which he insists upon such a chance could never be taken.

My interest in this question dates back to 1935 when I read an article by Dr. M. R. Robinson, now dead, of New York City, which impressed me as illustrative of a great clinician with an enviable background in the basic sciences of pathology and physiology. The title of the article was "The Surgical Treatment of Ovarion Dysfunction." It was published in the *American Journal of Obstetrics and Gynecology*, Volume 30. In October, 1940, I reported in the Memphis Medical Journal the history of a 13 year old girl who was treated with endocrine products of various sorts and a curettage. In spite of this a good deal of her time was spent in bed preventing her from going to school because of uncontrollable bleeding. Acute appendicitis forced our hand, and through a McBurney incision the oyster type of ovary three times normal size was discovered on both sides. She being thin allowed this extensive exploration through the incision. Both ovaries were "wedge-resected" removing about one third. Her recovery was complete and she has since had several children. Dr. Robinson made this observation, "If a dysfunction repeats itself too frequently and forcibly, or if it persists for too long a time the initial imperceptible structural alterations will ultimately develop into definite and permanent organic entities requiring surgery." He further observes that ovarian dysfunction with a hypo- or hyperovarianism may later become organic in some instances either unilaterally or bilaterally. The Stein-Leventhal syndrome may be associated with amenorrhea or excessive bleeding and, in addition to this, the more annoying and uncontrollable symptom of hirsutism. Dr. S. Shippel of the University of Witwatersrand, South Africa, undertakes to analyze the histologic changes in the ovary and attaches great significance to theca cell activity. He refers to this ovarian dysfunction and hirsutism as the hyperthecosis syndrome. Very little improvement of the hirsutism follows resection even though menstruation often returns to normal and fertility is established.

Dr. Davis has pointed out the difficulty of differential diagnosis of hirsutism and suggests the use of cortisone to observe the effect since improvement would follow if it is due to adrenal hyperplasia. I wonder whether the determination of 17-ketosteroids as a basic test which he also employed might not suffice.

The description of the ovary agrees with the description of observers in general but he also says the ovary may not be enlarged. How is it diagnosed?

The importance of this presentation is emphasized in my mind by a phone consultation with a surgeon which was too late. He reported encountering ovaries described by him as typical of the Stein-Leventhal syndrome and which he removed in toto from a 21 year old amenorrheic girl because of a fear of ovarian malignancy. While the condition will not be encountered often by any one surgeon, the recognition of the typical ovary is not difficult. Dr. Davis has performed a good service in reporting his experience.

Dr. O. J. Potthast, San Antonio, Tex. This is of great interest, and I recall a monograph that I had almost forgotten by the late W. Blair Bell of England. ("The Sex Complex," 2nd ed., Wm. Wood & Company, page 183). He was writing on endocrine disorders. That was before the days of our knowledge of how to test properly our endometrial biopsies. He talked of hyperovarian activity and advocated partial resection of ovaries.

Some years ago Dr. Karnaky talked about multicystic ovaries and the use of large doses of stilbestrol in the young women having excessive bleeding. Since that time I have had some good results by following his recommendations. I have hesitated only in the unmarried brunettes in giving the big doses of stilbestrol because of the darkening of the nipples and marking them with the stigma of a possible previous pregnancy. In the blondes I have not hesitated and have gotten very good results. I call attention to this procedure because it is a great help in resting the ovaries for a couple of months, and it seems as though we get a better ovulation thereafter.

I have done the wedge resection only in a couple of cases, but in the old days, I remember even in my intern days "way back yonder," when many of the doctors were puncturing these ovaries and apparently getting good results. Early in my practice I also did that and got some good results. But the wedge resection, of course, is much more logical.

I think the doctor is to be commended for bringing this subject before us. It is something that has not been brought out and it should be. It certainly is a well worth-while presentation.

Dr. Davis (Closing). The minute subcortical cysts that are concentrated away from the hilus over the dome of the ovary are the type of cysts that I have been referring to. In these ovaries, there may be 30, 40 or 50 of these very minute cysts. It is not a typical Stein-Leventhal ovary that has a large retained Graafian follicle or a corpus luteum in it. I think this syndrome is much more specific than a lot of people believe. I think besides these multiple cysts one has to demand that the ovaries have a thick capsule, that the ovary is not globoid but maintains its normal shape. I do not think that the type of thing I am talking about is a "garden variety" retention cyst of the Graafian follicle type.

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A Clinical Study of the Rh Factor*

CARROLL L. WITTEN, M.D.,† *Louisville, Ky.*

Erythroblastosis fetalis remains a serious threat not only to life in the predisposed infant, but at times is even more distressing in the permanent complication of kernicterus. To anticipate this emergency situation in the newborn is the responsibility of the attending obstetrician.

MOST OF THE STUDIES OF THE RH FACTOR and its complications begin with a history of the recognition, identification, and explanation of the cause of erythroblastosis fetalis originating with the work of Levine and Stetson[1] and of Landsteiner and Wiener.[2]

It will be the assumption here that everyone is sufficiently familiar with this historical background, and therefore the time will be used to deal with the current status and a clinical study of the Rh factor and its relationship to hemolytic disease in the newborn.

The some fifteen years that have lapsed since the important initial works of the aforementioned investigators have seen the increased development of tests for blood groupings and subgroupings, antibody titers, Coombs tests, exsanguination exchange transfusions, and other procedures for diagnosis and treatment of the results of Rh incompatibility.

There has even been developed an entirely new field of hematology known as immunohematology. It has been found that antibodies occur against platelets in a manner very similar to that in which newborn hemolytic disease occurs with resultant manifestations of thrombocytopenic purpura. The possibilities that antibodies against white cells may occur is under investigation and would, if found to be true, have far-reaching effects on the entire field of hematology.

It has been reported by Hsia and Gillis[3] that hemolytic disease due to blood groups A and B incompatibility is more common than previously thought and more frequent than that due to Rh incompatibility. The condition as a result of A and B incompatibility is generally milder but may present serious complications similar to that of Rh incompatibility including kernicterus.

It has been stated by Beard,[4] hematologist of Louisville, that "as far as is now known there are some 486,000 possible blood group incompatibilities and that, in theory, all of these can produce jaundice, but in reality only about 5 per cent do."

Rh Factor

In spite of these facts this paper will deal only with the Rh factor and the results of its incompatibility. The clinical significance of the Rh factor (known also as the D or Rh_o factor) became evident with the recognition of erythroblastotic infants as a result of mother-father differences in blood grouping. In the very vast majority of cases of erythroblastosis fetalis the mother is Rh negative and the father Rh positive. It has been postulated that during the latter third of pregnancy, when a thinning of the chorionic villi occurs, there are minute amounts of fetal blood cells that find their way into maternal circulation. It is this that serves as a stimulant to the mother's blood to produce Rh antibodies which readily pass into the infant's circulation, with subsequent destruction of the fetal Rh positive blood cells and resultant erythroblastosis fetalis.

Investigators have identified a basic group of six related factors, commonly referred to as the Rh-Hr system. These have been variously designated by Fischer and Race as D-d, C-c, and E-e, while Wiener used the symbols Rh_o-Hr_o, rh′-hr′, rh″-hr″. Each factor has been identified by means of a specific antibody, produced in individuals immunized by pregnancy or transfusions. The antibody formed most frequently is the anti-D (anti-Rh_o) which reacts with 85 per cent of the white popula-

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tion of the United States and thereby reveals D (Rh_o), the original Rh antigen[5] (Table 1). It is due to this fact that the terms "Rh positive" and "Rh negative" have therefore come solely to refer to the presence or absence of D (Rh_o) and clinically may be so considered. Patients who carry C (rh') or E (rh") but lack D (Rh_o) are always listed as Rh negative; however, for purposes of donating blood, an individual should be considered Rh negative only when he lacks all three factors.

Immunization of Rh negative individuals may occur in the following ways: first, transplacental immunization of the Rh negative mother by an Rh positive infant, and second, by transfusion or intramuscular injection of an Rh negative individual with Rh positive blood. The most severe cases of erythroblastosis fetalis usually occur in women who have been first immunized in this manner.

In Rh negative pregnant women who have been sensitized to the Rh factor, the titers of Rh antibodies in maternal blood specimens are closely correlated with the manifestations of erythroblastosis fetalis. This fact is strongly borne out in a study of 500 Rh negative pregnant women by Wiener, Nappi, and Gordon.[6] However, only Rh positive babies are affected. Even so, an occasional baby may be stillborn although the maternal Rh antibody titer is low, or an occasional baby may survive when the titer is high. To the authors these facts seemed to indicate that the baby's resistance to the antibody may also be important. If the maternal titer is relatively low, usually considered under 1:64, and there have been no previous erythroblastic infants or injections of blood, the chances of baby's survival are good.

Postnatal case finding is certainly not adequate to diagnose hemolytic disease due to Rh incompatibility, since severe forms of the disease require immediate attention at the time of delivery, and in many cases delivery and care of an affected newborn must be planned well in advance of delivery. Crucial time may therefore be gained by having Rh typing and serologic determinations in advance of delivery.

There is no doubt that every prenatal patient should be tested with anti-D serum in the present knowledge of the Rh factor and its significance in the pathogenesis of erythroblastosis fetalis. That this simple test should be done seems only logical, and yet a recent inquiry by me, of various doctors having delivered jaundiced infants in the past two years, revealed that a few did not do or have not done Rh typing on prenatal patients. They relied solely on the expected clinical appearance of the newborn and on the results of Coombs testing of the newborn. This seems to be a dangerous position to assume and can only lead to complications and a lower fetal salvage rate. It seems that we might all adopt a modification of some such procedure as has been set forth elsewhere.[7]

TABLE 1

THE SIX BASIC Rh-Hr SERA
Incidence of Reactions and Frequency of Production

Nomenclature Fischer-Race	*Wiener*	*Percentage*		*Occurrence of Pure Antibody in Immunized Women*
anti-D	anti-Rh_o	85	15	Frequently
anti-d	anti-Hr_o	63	37	Very rare
anti-C	anti-rh'	70	30	Very rare
anti-c	anti-hr'	80	20	Occasional
anti-E	anti-rh"	30	70	Occasional
anti-e	anti-hr"	97	3	Rare

Rh Testing in Obstetrical Cases

1. Every patient on the first visit,
   - A. Blood group (A, B, AB, O)
   - B. Rh typing.
2. Rh negative primiparae,
   - A. Determine blood group and Rh genotype of husband.
   - B. If husband is Rh positive:
     - a) Test patient's serum for presence of antibodies. (Concerning this point, there is a wide variance of opinion as to how early in pregnancy, or how frequently the blood of the Rh negative female should be examined for Rh antibodies. But there is evidence to suggest that serologic titer determinations should be obtained in the first pregnancy as well as in subsequent ones, since iso-immunization may occur. The seeming consensus of present opinion is that it is safe to limit the examination for antibodies to a single determination at or just after the 34th week of pregnancy in Rh negative women with no previous history of affected children and with no history of blood transfusion.)
     - b) Routinely perform direct Coombs test on cord blood of infant immediately following delivery.
3. Rh negative multiparae,
   - A. Determine blood group and Rh genotype of husband and surviving children, if any,
   - B. Follow procedure outlined in section 2 for Rh negative primiparae.

4. Rh positive patients with history of blood transfusions or intramuscular injection of blood,
   A. Determine Rh genotype of patient,
   B. Determine blood group and genotype of husband and surviving children, if any,
   C. Test mother's serum for antibodies against a panel of cells containing those present in the husband's blood, but lacking in the patient,
   D. Direct Coombs test on infant's cord blood immediately following delivery.
5. Rh positive patients with history of fetal or neonatal deaths, early jaundice or neonatal anemia.
   A. Follow procedure outlined in section 4 above.

A routine Rh typing and antibody determination offers the physician and the patient several tangible advances:

1. Prevention of severe and fatal transfusion reactions in patients already immunized either by previous transfusions or by pregnancy.
2. Increased salvage of the erythroblastotic infant.
3. Prevention of accidental immunization of Rh negative individuals by transfusion or injection of Rh positive blood.
4. Pregnancy wastage may be avoided in some cases.

In those mothers in whom no anti-Rh antibody is demonstrable during the last month of pregnancy, one can with justice expect no hemolytic disease in the newborn due to Rh incompatibility.

Erythroblastosis Fetalis

It might be proper to mention at this time that initially the Rh factor received widespread publicity in the lay press and created many unfounded fears that have been only surpassed in extent and scope by the flying saucer and the Salk vaccine. The well-informed physician is in an excellent position to allay the fears of his patient by advising her that:[8]

(1) The Rh factor is a normal variation, just as is eye or hair color, and is inherited.

(2) Rh incompatible mating can occur in only 13 per cent of all marriages, i.e., an Rh negative wife 15 per cent and an Rh positive husband, 85 per cent, (15 per cent times 85 per cent equals 13 per cent).

(3) In incompatible mating about 50 per cent of the Rh positive fathers will be heterozygous so that half of the offspring may be Rh negative and therefore unaffected, thus further lowering the chances of incompatibility to 7.5 per cent.

(4) The vast majority of Rh negative women do not produce anti-Rh antibodies. Rh negative women who do produce antibodies as a result of pregnancy with Rh positive children will usually first have at least one or two unaffected infants.

(5) The actual incidence of erythroblastosis in all matings is only about one in two hundred (1:200) full-term pregnancies, and in incompatible matings is one in about twenty-six (1:26) full-term pregnancies with many of these being only mildly affected.

(6) The prognosis for affected infants is much better with application of recent knowledge.

And, to the list, we might add a seventh fact:

(7) Approximately 10 per cent of the Rh positive babies will be normal even after a patient has delivered one or more severely damaged infants.[9]

A study was made at St. Joseph Infirmary in Louisville to ascertain the percentage of erythroblastosis fetalis to the total number of births. It was found that in the two year period of 1953-54 there were 4,769 deliveries, of which 31 were diagnosed as erythroblastosis fetalis for a percentage of 0.65, which is comparable to the percentages reported elsewhere (Table 2).

It was found that of the 31 cases of erythroblastosis fetalis, 2 were stillborn and that 26 of the 29 remaining were treated by exsanguination and transfusion. The three not given exchange transfusions were mild cases proven by a positive Coombs test and all improved and lived with no identifiable sequelae on discharge. Of the 26 that were given exchange transfusions three died, for a mortality rate of 10.4 per cent of live births with erythroblastosis fetalis, or of 16.1 per cent of total cases of erythroblastosis fetalis. This survival rate compares very favorably to a mor-

TABLE 2

INCIDENCE OF ERYTHROBLASTOSIS FETALIS*

Years	*Total Deliveries*	*No. of Erythroblastotics*	*Percentage*
1953 and 1954	4769	31	0.65

*St. Joseph Infirmary, Louisville, Kentucky

TABLE 3

MORTALITY RATES OF ERYTHROBLASTOSIS FETALIS*

		Died	*Percentage*
Live births with eryth. fetalis	29	3	10.4
Total births with eryth. fetalis (including 2 stillborn)	31	5	16.1

*St. Joseph Infirmary, Louisville, Kentucky

tality rate, prior to the use of exchange transfusions, of 50 to 60 per cent (Table 3).

Considering the total 4,769 births in this two year period, 1953-54, there is a resultant death rate from erythroblastosis fetalis of only 0.10 per cent (Table 4) which seems very satisfactory and comparable to results submitted elsewhere.

The figures in table 4 are further proof that erythroblastosis fetalis occurs in only a fraction of those cases in which it is possible. The combination of an Rh positive infant and an Rh negative mother is being found in about 8 per cent of pregnancies, whereas laboratory evidence of erythroblastosis fetalis is present in only about 0.6 per cent of pregnancies (Table 2).

The ideal treatment of the erythroblastotic infant would be prevention of the condition. However, attempts to prevent erythroblastosis fetalis have been fruitless and there is a long list of measures that have failed. So far as one can find out there are only two drugs that are still under trial in the antenatal management of the disease. One is Rh hapten. The other is cortisone. The data available to date fails to reveal that either of these are helpful in their attempt to prevent the condition.[10]

Some years ago the premature induction of labor was proposed as a method of preventing erythroblastosis fetalis and its complications and this procedure became quite popular. As a result, a virtually uncontrolled mass experiment in this procedure occurred. In 1946, however, Vaughan[11] suggested that early induction might contribute to the development

TABLE 4

DEATH RATE FROM ERYTHROBLASTOSIS FETALIS TO TOTAL DELIVERIES*

Deliveries in 1953-54	*Deaths from Eryth. Fetalis*	*Percentage*
4769	5	0.1

*St. Joseph Infirmary, Louisville, Kentucky

of kernicterus. In a later paper Vaughan[12] and associates presented evidence that kernicterus was directly related to the degree of immaturity of the erythroblastotic infant. Mollison and co-workers[13] came to the same conclusions in a carefully planned survey. Primarily due to the work of these two men, the procedure of premature induction of labor in an expected case of Rh incompatibility fell into disrepute.

Prematurity uncomplicated by erythroblastosis fetalis is the main cause of neonatal deaths. When this condition is coupled with prematurity a serious therapeutic problem exists. Therefore, at present, the only successful management of this condition revolves about early and adequate exchange transfusions for the newborn. Transfusions should continue with Rh negative blood as long as the Coombs tests are positive.

In doing the exchange transfusions, one must try to keep the plasma bilirubin below 20 mg. per 100 cc. Under these conditions a report of 97 cases of erythroblastosis fetalis seen before the twelfth hour demonstrated an over-all mortality of only 8.3 per cent, and no child in this series that survived had recognizable neurologic sequelae.[14]

If facilities for immediate exchange transfusions are available, the obstetrician can aid in preventing complications by seeing that the expected erythroblastotic infant does not receive the full complement of placental blood by clamping off the cord in a manner to prevent this. This decreases the amount of abnormal blood pigment which, if allowed to enter the infant, must only be removed later by exsanguination.

If treatment is prompt, and if the blood pigments are controlled by exchange transfusions, and if the special disturbances that may be encountered are anticipated, the challenge presented by the erythroblastotic infant may often be met successfully.

At this time the recent development of a blood warming Rh transfusion device at Schenectady, N. Y. should be mentioned. It was invented to lessen the shock which newborns are subjected to during exchange transfusions. Still to be answered are such questions as to whether the cold blood used has been a significant factor in the 10 per cent of deaths, and whether the warm blood will reduce the

percentage of fatalities. Current indications are that blood temperature is a factor and that in some cases may be the deciding factor.

Summary

In summary, this has been a review of generalized considerations of the problem of Rh incompatibility, with emphasis on the current status of this important problem.

A series of deliveries over a two year period was examined to ascertain the incidence of Rh incompatibility as well as the mortality from this condition. These percentages are then compared to the theoretical incidence of hemolytic disease of the newborn due to Rh sensitization.

The importance of prenatal Rh typing on every patient, and of antibody titer testing on those found to be negative with an Rh positive husband is stressed, and a suggestion for a routine procedure under various circumstances is presented. If antibody titers are found to be present it is suggested that preparation should be made for possible exchange transfusions.

One is urged to use the Coombs test on each newborn from an Rh negative mother and Rh positive father. And the finding of a positive Coombs test should be considered as pathognomonic of erythroblastosis fetalis, at which time proper measures should be instituted by exchange transfusions to treat this condition, if indicated. One should know well in advance of delivery of the possible presence of hemolytic disease of the newborn since crucial time may be gained or lost.

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Discussion (Abstract)

Dr. J. F. Lucas, Greenwood, Miss. Obstetricians had the Rh factor thrust into their everyday consciousness by the discovery in 1941 that this factor was related to the occurrence of post-transfusion hemolytic reactions, and the appearance of erythroblastosis fetalis in infants of sensitized Rh negative women.

A period of confusion followed like that accompanying any discovery when the extent of its application is uncertain; technics involved are still imperfect and trained personnel is scarce. The phase is now over, at least for the most part, and has left us with facts and technics that make it possible to recognize and avoid the errors unwittingly committed in the past, anticipate certain happenings, and have a measure of success in preventing or correcting them.

The literature dealing with the Rh factor is so voluminous that even the experts who work with the problem have difficulty keeping abreast of it. We certainly owe a debt of gratitude to Drs. Levine, Stetson, Landsteiner and Wiener for their pioneer work in this regard. Other investigators following up in this research are rapidly discovering other incompatibilities which hold promise of explaining some of the rare cases of hemorrhagic disease of the newborn not due to the Rh factor. Practical applications will no doubt rapidly follow these new discoveries that will rebound to the benefit of the practicing obstetrician and his patients.

Dr. Witten in a masterful, clear and concise presentation has pictured the practical application of the knowledge of Rh factor developed over the past 15 years and made recommendations that should be standard practice of all men accepting the responsibility of caring for pregnant women. The procedure of Rh testing in obstetrical cases as outlined by the essayist should be mandatory in every hospital and obstetrical clinic.

In discussing this paper I am at a loss to find anything to be critical about and will use the time allotted me on the program to stress a few points he has mentioned.

Erythroblastosis caused by Rh incompatibility is rare in the first pregnancy, in the absence of previous sensitization of blood, which was not an uncommon procedure 15 to 30 years ago in the attempt to prevent or treat hemorrhagic disease of the newborn. Sensitization in multipara appears to be frequent in women with a history of delivery by cesarean section, of induced abortion, of premature separation of the placenta, and of long complicated labor. Any of these conditions would promote entrance of fetal blood into the maternal circulation. It is believed that unless a woman is sensitized prior to onset of pregnancy, erythroblastosis, if it occurs at all in that pregnancy will usually be mild.

I feel that all prospective parents should be tested for Rh incompatibility and that every Rh negative female, regardless of parity, should have three antibody tests during pregnancy,—one at about 16 weeks, another at 28 to 32 weeks, and a third at 34 to 36

weeks. The first test provides a base line from which to judge the subsequent course of the titer. The second test serves to put the parents and obstetrician on guard for a possible intra-uterine death, and the third test will pick up most serious sensitizations which may occur late in pregnancy.

We feel that it is hazardous to postpone serologic examinations until the last few weeks of pregnancy because intra-uterine death may occur at any time. This unhappy event is accompanied by three potential dangers to the mother which must be regarded seriously. The first is that of the emotional shock which may follow the loss of a baby even though it is nonviable. The physician should not allow parents to face tragedy without adequate preparation. There is also the possibility of a rapid developing polyhydramnious with lowering of maternal serum protein as well as serious hemorrhage resulting from disturbance of coagulation factors.

It is generally believed that titration of the antibodies will give one an idea how severely the patient is sensitized, but this has not always proved true. A patient with antibodies in a dilution of 1:32 may have an erythroblastic stillborn and another one with antibodies in a dilution of 1:256 or higher may have a normal infant. The author's suggestion that the baby's resistance to the antibody may be a variable factor.

In the early years when tests for antibodies revealed a sudden rise of titer, it was advocated by some that the pregnancy should be interrupted to prevent further damage to the infant by removal of the fetus from further action on the maternal antibodies. As a result cesarean section was frequently advocated to terminate these pregnancies since very few of them could have labor successfully induced. These infants fared very badly and many developed kernicterus. The fetal mortality was much higher when prematurity was a complicating factor. The pendulum then swung to the opposite direction and until recently, it was the consensus that early delivery was contraindicated. In the last two or three years the success of exchange transfusions in preventing kernicterus has led to such a modification of opinion that in a few hospitals, all Rh sensitized pregnant women are delivered if possible at 37 to 38 weeks. Excepting the hydrops form of erythroblastosis, these babies seem to have some protection as long as they are in the uterus, and in my opinion should be allowed to go to term and go into labor spontaneously. The one exception is the patient in whom fetal death took place a few days before term, should possibly be induced at the thirty-eighth week.

In the usual case, if Rh negative mother shows the presence of Rh antibodies, it is best to let her continue to term and go into labor spontaneously. Five hundred cc. of type 0 Rh negative blood which has been cross-matched with the mother should be ready for use, should the baby show signs of erythroblastosis. Cord blood should be obtained for Coombs test, bilirubin, Rh determination, and complete blood count. The cord is left 4 inches long and wrapped in wet saline sponge. If the Coombs test is positive and the baby reveals any clinical signs of erythroblastosis or a hemoglobin of 15 grams or less, he should be transfused immediately, preferably by exchange transfusion. Repeated exchange transfusions are indicated to keep the bilirubin below 20 mg. per 100 cc. in order to prevent kernicterus.

Aside from early delivery, the physician is occasionally called on to consider therapeutic abortion in cases of Rh incompatibility. In view of the variability of the disease and the recently improved methods of treatment, therapeutic abortion is certainly not to be considered.

Dr. Richard Paddock, St. Louis, Mo. I would like to thank Dr. Witten, on behalf of everyone here who does obstetrics for this excellent presentation. The Rh system in its simplest form, at best, is confusing to most clinicians.

A number of important clinical points have been mentioned and stressed in this paper. He calls our attention to the fact that there are many new developments in the field of immunohematology. He quotes one hematologist as saying there are as many as 486,000 possible blood group incompatibilities. This is something to think about when giving a transfusion, for we all know that there may be adverse reactions even though the blood set-up checks perfectly both before and after the transfusion is given.

The exact mechanism of the production of Rh antibodies in pregnancy is still unknown. However, we know that it occurs, sometimes when least expected, and again it may fail to occur when most expected.

The working out of the six basic sera of the Rh-Hr sera system is an achievement worthy of endless praise, although it may seem very confusing to the clinician.

If we would follow the recommendations of Dr. Witten, I am sure we would be in a much better position to effect fetal salvage in a number of Rh incompatible cases. The strong point for us as clinicians is to have the Rh typing and serologic determinations well in advance of delivery. Having this worked out according to Dr. Witten's title of *Rh Testing in Obstetrical Cases,* we should be prepared for any eventuality following birth which, as he emphasizes, includes facilities for exchange transfusion and immediate examination of fetal blood, even though the newborn child may not show any evidence of distress.

I am glad to see that the author mentions the adverse results obtained in the premature induction of labor. I have always felt that this procedure only added insult to injury in the anticipated erythroblastotic baby, as well as adding a major problem in the life of the premature child that did not turn out to be erythroblastotic.

Blood disorders of the newly born account for about 5 per cent of perinatal mortality. Despite the fact that Rh hapten and cortisone have little to offer in the prevention and treatment of erythroblastosis, we should avail ourselves, as the author summarizes, of all the known methods for the institution of treatment in the erythroblastotic child.

Dr. Wilbur E. Hoffman, Charleston, W. Va. In the middle thirties a patient was referred to me at term bleeding without pain. A diagnosis of placenta previa was made and an immediate cesarean section performed. The baby, who was very large and edematous was stillborn. The placenta covered the internal os and filled the lower uterine cavity. The placenta was about five times the size of the average placenta in circumference and about four to six inches thick and yellow.

This was my first experience with such a condition; neither the pathologist at our hospital nor I recognized the condition for what it was. In 1941, Levine published his first article in the J.A.M.A. on the Rh factor and the same year another article appeared in the "Gray Journal."

The West Virginia State Health Department (Maternal and Child Welfare Division) sponsored throughout the state a Seminar on Obstetrics in 1941 or 1942. We had outstanding obstetricians and pediatricians speak at these meetings. Dr. Lee Palmer, pediatrician of Louisville, spoke at one of these meetings and talked about erythroblastosis describing the three conditions of the newborn. It was then that I realized what I had encountered several years before and did not know what I was seeing.

After we started doing the Rh test on all our patients a specimen of Rh negative blood was sent to Dr. Levine for interpretation. Through his analysis he found one of my patients with Kiel blood. This patient has sent some of her blood to Philadelphia and Pittsburgh when doctors have asked Dr. Levine for Rh negative Kiel blood.

Since May 1955, I have delivered six babies from Rh negative mothers, the babies had a positive Coombs test, low hemoglobin and low red blood count. All these cases were delivered two to three weeks early by rupture of the membranes. Some of these mothers had lost one or two babies in utero and in others the babies died from one to seven days after birth. They were all multipara. Dr. Zekan at our hospital gave these babies a direct exchange blood transfusion through the umbilical cord. One baby was given three transfusions before it left the hospital. We have been very fortunate with our results.

In these Rh negative mothers it is the obstetrician's duty to watch for discoloration of the amniotic fluid, enlarged liver or spleen of the baby, color of the baby, get a Coombs test and blood count, and be prepared for an exchange transfusion.

Dr. Witten (Closing). There are many facets of the Rh factor problems that one could discuss pro and con. I, not being an expert in the field, am rather happy that there were not a lot of questions concerning it. The audience has been most kind in this respect as well as in their attention.

I should like to close by saying only this, that I have been very pleased with the hospitality in Houston throughout the meeting and especially with that of the Obstetrical Section. I should like to thank Dr. Lucas, Dr. Paddock, and Dr. Hoffman for their very excellent discussion. I should also like to thank the secretary of this section, Dr. Robert F. Monroe, for his great kindness and considerate help throughout this meeting.

Medical Journalism in 1848

. . . The general plan of the original periodical publications which have been enumerated is very similar. The first part of each number is devoted to original articles, consisting of essays, histories of epidemics and endemics, series of cases, and single cases, and accounts of operations. Occasionally a more detailed and comprehensive history of some disease is introduced under the name of *monograph*, and not unfrequently extensive statistical tables are given, bearing especially upon surgical and obstetrical practice. Then follow *Reviews* or formal examinations of works recently published, usually analytical in character, and having for their principal object the book rather than the general subject of which it treats. To this division succeeds a miscellaneous and heterogeneous assemblage of *bibliographical* notices; the sweepings of the critical *atelier;* the rinsings and heeltaps of the critical banquet; a necessary part of the editor's prospectus, but one which is least gratifying to minute inspection. Here the importunate friend receives his expected compliment, the dull dignitary is pacified with his scanty morsel of eulogy, the Maecenas is paid in fair words for his patronage; the book which must be noticed and has not been read, is embalmed in safe epithets and inurned in accommodating generalities. Lastly, a considerable part of the number is made up of selections, either taken promiscuously from other journals and recently published works, or in the better managed periodicals classified so as to present a summary of the recent progress of science in its several departments.

The proportion allotted to these several divisions varies very much. Taking into consideration the usual difference of type in the original and borrowed matter, and the very liberal extracts which the reviewers commonly make from the work before them, it will be found that a very large part of all the journals is made up of quotations; and to a considerable extent of the same quotations, whatever may be the particular journal examined. The committee have been struck with the fact, that the same articles have been presented over and over again to their notice, in many different periodicals, each borrowing from its neighbours the best papers of the last preceding number, so that the perusal of many is not so much more laborious than that of a single one, as would be anticipated. The ring of editors sit in each other's laps, with perfect propriety, and great convenience it is true, but with a wonderful saving in the article of furniture.

—From the report of the committee on medical literature. *Transactions of the American Medical Association*, Vol. 1, 1848, pp. 255-256. The committee was composed of Oliver Wendell Holmes, Enoch Hale, G. C. Shattuck, Jr., D. Drake, John Bell, Austin Flint and W. Selden.

An Attitude Toward the Clinical Management of Erythroblastosis Fetalis*

HARRIET M. FELTON, M.D.,† *Galveston, Tex.*

The author considers this disease from the clinical rather than the laboratory viewpoint concerning decisions as to whether to transfuse or not to transfuse.

ERYTHROBLASTOSIS FETALIS, A SO-CALLED "LABORATORY DISEASE," is still shrouded with some mystery as far as most physicians are concerned. The majority of the case reports have come from large medical centers where laboratories are well equipped and the personnel highly trained in managing the situation created by the potentialities of an erythroblastotic infant. The accepted treatment of exchange transfusion has been developed under the guidance of physicians who have also used their laboratory findings to establish the various steps in the diagnosis of this complicated disease. There are, however, many clinicians who do not have access to all of these advanced aids and who cannot obtain the highly specialized technical reports which are so helpful when lifesaving decisions must be made. In many instances it is impossible to transfer the patients to large medical centers in time to make the specific diagnosis and provide efficient treatment. It might be wise, then, to think about this disease in a less elaborate manner and to discuss diagnosis and management from a more clinical aspect.

Diagnosis

The diagnosis of a severely diseased erythroblastotic baby is not difficult at birth. The amniotic fluid and sometimes the tissue fluids may be stained deep yellow or green. The infant may be edematous or have other signs of hydrops fetalis. He may be pale and show signs of a mild or severe shock as is often seen in babies with anoxia. The real problem arises in diagnosing early the presence of the disease process, or predicting the possibility of its appearance in the baby who appears to be in good condition at birth. Unfortunately, many erythroblastotic babies appear normal at birth and it is very difficult to teach interns, residents and other hospital personnel that these babies may be in serious trouble or even dead in a matter of hours unless swift preventive measures are taken. It has been shown that early exchange transfusion has substantially lowered the mortality rates in this disease.[1] How then can the diagnosis be made quickly enough and the decision be made to institute immediate exchange transfusion in the appropriate case?

Every physician must be alert to the possibility of the development of erythroblastosis. After delivery his first duty is to examine the baby thoroughly. If the disease is even remotely suspected, the cord should be cut immediately 2 or 3 inches from the abdominal wall, without allowing excess pulsations. The baby should be handled in the routine manner as far as resuscitation and administration of vitamin K and external heat are concerned. The presence of pallor, poor peripheral circulation, enlargement of the liver and spleen would indicate haste to obtain confirmatory laboratory evidence of the disease. It is important to stress the fact that jaundice, true jaundice, is not present at the moment of birth and only appears as the baby's circulation becomes established and the capillary bed fills. Therefore, when the baby is three or four hours old, a slight icteric tint begins to be seen around the fold of the lip, the chin and the nose. Deep jaundice is gradually more noticeable and usually is well established within 24 hours unless the baby is

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treated. Blood must be obtained from the baby immediately for a complete blood count, Rh typing and Coombs test. These procedures are now relatively simple and should be a routine in all hospital laboratories. Pediatricians should be proficient in each of these studies and be able to advise any laboratory technician on the proper interpretation of the test results. Serum bilirubin determinations at the time of delivery and periodically thereafter may serve as a guide to therapy.[2] A crude method for determining serum bilirubin level is to spin down a sample of the baby's blood and observe the color of the serum and to keep this for later comparison. It has been said that the color of the serum will roughly correlate with the depth of jaundice which will be seen in the baby's skin after about 18 to 24 hours if the baby has not been treated. Recently, Abelson and Boggs[3] have described another blood pigment in sera of babies who have signs of severe damage at birth or who are developing signs of disease at some time after delivery. The presence of this pigment is shown grossly by a brownish or greenish color of the baby's serum, and in the laboratory is measured by the absolute optical density near 415 mu as seen by the examination of the baby's serum in a Beckmann spectrophotometer. This is a new technic which is available in only a few laboratories. Until the procedure is more generally used, the blood count, Rh type, Coombs test and serum bilirubin are the only guides to the physician's clinical judgment in evaluation of the baby.

In any case in which the clinician is satisfied with the condition of the baby, and with reliable laboratory reports showing an Rh negative baby or a Rh positive baby with a negative Coombs test, the original concern may be somewhat relaxed. The baby should be watched closely, however, for 24 or 48 hours for complete safety. In case of doubt, blood counts and serum bilirubin estimations ought to be obtained daily for the first 72 hours to provide double assurance to the clinician that his judgment has been correct.

It might be noted that confusion often arises when a blood count is reported showing normal hemoglobin and red cells, but with an abnormal degree of erythroblastemia following a delivery by instruments or after a long labor. Fetal asphyxia or other stress situations surrounding delivery notoriously produce an abnormal number of nucleated red blood cells, but these forms disappear very rapidly over the first 8 to 12 hours of life. The report of hemoglobin over 15 or 16 grams and a red blood count of 5 million or more with a normal differential count, even if the baby is Rh positive, will not entirely exclude the presence of severe damage from erythroblastosis. If the Rh positive baby has a good erythrocyte count and no evidence of enlargement of the liver or spleen and, in addition, is the first baby of an Rh negative mother who has had a good obstetrical history, immediate exchange may be deferred. Any such infant must be closely followed by blood counts every 8 to 12 hours and by frequent physical examination with particular attention to the neurologic evaluation. If the blood count shows red cell destruction with or without early red cell forms and the neurologic signs do not change, this baby need not be given an immediate exchange transfusion.

If the count falls below three million, a small transfusion may be given. One must not allow the blood count to fall dangerously below the efficient oxygen carrying level. If any baby under suspicion shows any change in his neurologic status, even though his blood picture has not altered, he must be given an immediate exchange transfusion. In cases with a history of previous miscarriages, incompatible transfusions reported by the mother or jaundiced siblings, an Rh positive baby with a normal count and physical findings should be given immediate exchange transfusion to prevent the onset of expected severe complications. Premature infants with any evidence of erythroblastosis fetalis must have an exchange transfusion as soon after birth as possible.

When one follows the course of a number of babies with erythroblastosis from a purely clinical viewpoint, it is possible to diagnose a baby with severe erythroblastosis at birth and also to predict impending trouble in a postnatal period of an initially normal appearing baby by recognizing the neurologic changes as they appear. After "sitting it out" with a few babies it becomes apparent that a consistent pattern or sequence of events occurs which reflects progressive damage from the

disease. These changes often begin within an hour or two after birth but are not usually present at the time of delivery. When prompt exchange transfusion is carried out these signs, if not allowed to progress too far, can be reversed and the baby be returned to its previous neurologic equilibrium. If these signs occur and are disregarded, the baby goes on to develop the irreversible condition known as kernicterus. In some babies with severe disease a single transfusion may reverse the signs, but they may reappear in a few hours. It is sometimes necessary to carry out the procedure two, three or even four times to save a baby from the fate of cerebral palsy or some other devastating neurologic sequelae. Often a physician makes the diagnosis of erythroblastosis and performs an immediate exchange transfusion. He then washes his hands, orders routine blood counts every four hours and small transfusions if the count begins to drop. In many instances the course of the baby is uncomplicated, but in some cases the doctor is quite surprised and dismayed the next day to find his charge with fists clenched, head back, eyes rolled up and choking. The original exchange transfusion should be only the beginning of a careful vigil, which must last until the baby is 72 hours old.

The danger signals are the neurologic findings. These should be looked for every two to three hours. The first sign is a slight but unmistakable change in the pitch of the baby's cry. Instead of the loud, lusty cry of the normal baby, he suddenly begins with a high, whining cry and then settles down into the normal range. In the matter of as short a time as 30 minutes, the character of his cry may have changed completely into this high range. Later when stimulated, he will make the facial motions of crying, but the actual sound is delayed. When it occurs, it is shrill, high pitched and progressively becomes more feeble.

As the cry becomes more high pitched, the rooting and sucking reflexes become depressed and finally disappear, and the baby may have some difficulty in swallowing. The Moro reflex is active fairly well along in this whole picture but gradually becomes less so, and by the time the baby is unable to "sound off" his cry the Moro reflex disappears or is very weak. The time element associated with the occurrence of these neurologic signs is variable, but it cannot be emphasized too strongly that once this sequence of events begins, it continues its course.

If we stand by long enough, say three to four hours, we will see a flaccid baby with a poor color, slightly irregular respirations, and regular rather slow heart rate. He does not respond at all or only slightly to stimulation. If we continue to stand by, this baby may continue this downward course, may develop hemorrhagic phenomena, respiratory difficulty and die. On the other hand, he may become restless and his flaccidity changes so that he begins to show progressive stiffness of his muscles rather than the previous relaxed condition. We now have a baby who lies with his eyes fixed or turned in one direction or another. He does not follow light or stimulation well. His thumbs are folded into his hands and soon his fingers close tightly into fists. He begins to extend his head backward, and when his heels are lifted from the bed, the entire plane of the back also lifts. He has no rooting reflex and his sucking reflex and swallowing reflex are very depressed. If this picture is apparent, the baby has undoubtedly developed the dread complication of kernicterus. Exchange or re-exchange transfusion at this time usually accomplishes nothing.

In attempting to correlate the appearance of the neurologic findings with changes in the blood picture or bilirubin levels, it appears that these signs precede laboratory evidence of severe involvement. Prompt replacement or re-exchange procedures in infants who have been under our care have halted the downward course and the progressive manifestations of the neurologic involvement. We have also been able to halt progression of these symptoms in babies who have gone as far as the state of the very faint or absent cry and very depressed reflexes. Frequently these babies are so sick that they are barely breathing and do not react in any way to the manipulations involved in the mechanical part of the procedure. Usually, about half way through the replacement procedure the baby begins to react. They struggle against their restraints, and by the time the procedure is over are complaining bitterly about the whole thing. This is a difficult picture to describe and hard to believe until a case has been ob-

served and followed as carefully as one must in order to pick up the timing of the neurologic findings accurately.

Management and Prognosis

The objective in the diagnosis and management of erythroblastosis is to prevent or reverse a disease process which otherwise would result in permanent neurologic damage. Babies with erythroblastosis now rarely die in the first three days of life as they so often did before the advent of exchange transfusions. The morbidity, however, continues to be high and our attempts to reduce these figures are certainly clumsy at the present time. Since the mechanism of this disease process is still obscure we are forced to follow a crude set of rules. As far as we know, the dangerous sequelae of this disease in most cases have evidently started before birth and rapidly accelerate after the baby is separated from its mother's blood supply. Some "toxic" substance or substances which are in the baby's circulating blood cause damage to the reticuloendothelial and central nervous systems. These substances also seem to cause continuing hemolysis although they themselves originally appear to be the product of some hemolytic process. Because of the apparent acceleration of the disease process immediately after birth, it is possible that the antenatal hemolysis differs in some way from that which occurs subsequently. The simple washing out of the baby's circulation at birth removes most of the major portion of this so-called "toxin." In mild cases one such irrigation is sufficient. In other cases, however, the continued hemolysis of red blood cells in the tissues or in the bone marrow may release sufficient additional "toxin" to reactivate the hemolysis. It is this type of case which needs the most skillful management.

Until such a time as we have a more reliable laboratory prognostic measure, we cannot predict the outcome of this disease in any baby at the time of birth. We cannot afford to stand by and let the symptoms become established. We can only know when we must act to prevent progression of the disease and take measures to reverse the process. The procedure of exchange transfusion in experienced hands is comparatively simple. If it is carried out carefully, with all safeguards preserved, the baby is not harmed. If one is in doubt, a careful exchange transfusion is the method of choice in contrast to indecision and a child with a damaged brain.

Clinical Material

The review of 51 cases of erythroblastosis fetalis or hemolytic disease of the newborn that appear in the records of the John Sealy Hospital, of the University of Texas Medical Branch, since 1947 shows the trends in therapy during these years. The distribution of these cases in shown in table 1. Ten cases were recorded before exchange transfusion therapy was instituted in this hospital. The two cases of kernicterus occured during this time.* There were no premature infants in this group. One cannot help but wonder whether some of these children are among the first 104 cases who were admitted to the Moody State School for Cerebral Palsied Children. Miss St. James, Drs. Hansen and Boelsche[4] have studied the histories and these show that 23 were known to have been jaundiced on the first day of life.

In reviewing the charts of the infants who died, the results with the premature group seem to be discouraging. The death wherein

*The word kernicterus in this publication refers to the irreversible neurologic signs found in infants or children who have had hemolytic disease of the newborn.

TABLE 1

ERYTHROBLASTOSIS THERAPY 1947-1955
JOHN SEALY HOSPITAL

			Single Exchange		*Multiple Exchange*		
Gestation Period	*Total*	*Small Transfusions*	*With ACTH*	*Without ACTH*	*With ACTH*	*Without ACTH*	*No Treatment*
Full Term	34	15	8	1	7	1	2
Deaths	7	3	1	1	0	0	2
Kernicterus	2	2	0	0	0	0	0
Premature	7	1	3	0	2	0	1
Deaths	6	1	3	0	1	0	1
Kernicterus	0	0	0	0	0	0	0

no treatment was given occured at one hour after delivery in an infant who had signs of hydrops fetalis. In regard to the babies who died after exchange transfusion it should be mentioned that they were not referred until after they were twelve hours old, indeed one was five days old. This fact serves as a grim reminder that prematurity is a great hazard and must be prevented if at all possible in potential cases of erythroblastosis. For success early diagnosis and exchange transfusion in these infants is mandatory.

Fortunately, the full term infants have a better record. From our data it is obvious that exchange transfusion is the treatment of choice. In analyzing the failures, two babies died without appropriate treatment, one who suffered hydrops fetalis, and one who was treated for sepsis and later diagnosed from the delayed laboratory reports. Of the infants who expired after exchange transfusion, one infant had severe hydrops fetalis and died six hours after birth, and one infant had in addition to hemolytic disease of the newborn complete volvulous of the small intestine.

The series reported here is too small to evaluate the supportive measure of the administration of ACTH. It has been used in this series as adjunctive therapy in all cases with signs of the disease at birth and in cases in which there seemed to be evidence of unusual irritability at any time during the first three days of life. The dose used is 5 mg. per Kg. per dose, given every six hours for 5 to 6 days. The usual precautions to prevent electrolyte imbalance, namely the use of a low sodium intake and the addition of potassium chloride after urinary function has been established, are followed.

Summary

Physicians must be constantly aware of the possibility of being confronted with an erythroblastotic infant. Plans for the management of this baby should be made in the prenatal period. There are no "ifs" or "buts" about this point. When early diagnosis has been made the baby must be observed for signs of impending trouble every three to four hours for 72 hours and appropriate measures taken as promptly as possible to prevent death or kernicterus, which in itself is a hopeless situation. The key to the solution of the problem is held by the practicing physician. Not only may he save the life of a child but also he makes it possible for the baby to become a happy, healthy individual instead of a seriously handicapped creature who must struggle for his every want.

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4. Personal Communication

Discussion (Abstract)

Dr. Roy K. Sanford, Perryton, Tex. I would like to ask Dr. Felton if there has been any work done in the subgroup incompatibilities causing erythroblastosis in this way. I mean, are babies with a strongly positive direct Coombs test, who are apparently not upset by the Rh factor, more apt to become erythroblastotic than the ones who have positive direct Coombs from the Rh factor, or are they less apt to develop erythroblastosis?

Dr. Felton. With sufficient laboratory aid at hand, I suppose you all realize that in our series we are in a peculiar position geographically. Many of these babies are referred to us, and the original laboratory data have not come with them and we are not able to get it. But we have had one baby with anti-lues A factor definitely established, and two babies with an ABO incompatibility in this group we are reporting. We understood that the anti-lues A factor is not supposed to be a dangerous one. This baby had a very strongly positive Coombs test and almost died before we could get the exchange started. The ABO babies we have known about have not been seriously affected.

Dr. D. W. Van Gelder, Baton Rouge, La. I should like to ask Dr. Felton about multiple exchange transfusions. In our experience, we can ordinarily recognize when a baby is erythroblastotic and can usually "exchange" them, but our problem has been, when to stop "exchanging" them? Two years ago, under the influence of the Boston group, we used the level of 20 mg. per 100 cc. bilirubin as a level and were disturbed when the level went above that. You, I am sure, have had the experience of exchange transfusing a baby with bilirubin level of 30 and immediately after the exchange the level drops back to, let us say, 8 or 10 mg. per 100 cc. However, two or three hours later, the level is already back up to 22 or 24. When should you stop "exchanging" such a baby? I noted you made the statement that you watched these infants very carefully for the first three days of life. After that time, do you feel it is safe to continue without "re-exchanging" these babies? That has been our problem.

We had one infant two years ago, to whom, on the eighth day of life, we gave the fifth exchange transfusion. I recall Dr. Abelson, two or three years ago,

reported one infant whom she had "exchanged" I believe five times also, because of the presence of abnormal bilirubin. Do you consider the interval of three days adequate? If you get by for this length of time there is not much likelihood of development of a subsequent neurologic defect.

Dr. Felton. In working with Dr. Abelson in Philadelphia before I came down here, I learned that if a baby does not show signs of progressive neurologic damage within the first three days of life, he is not going to have very severe kernicterus. The bilirubin level in our hands, I must admit we do not always have our bilirubin determinations because of the 48-hour-week and other factors, does not seem to hang together with our sickest babies. We have had levels anywhere from 3 to 43 right before the immediate exchange or before some of the re-exchanges in our most severely sick babies.

We have done exchange transfusion three or four times, but we have not had to do it after the third day of life since we have been following the examination of the baby's neurologic system. If we get into trouble, it is usually on the "re-exchanges" somewhere between 18 and 36 hours. We sometimes have to "re-exchange" them as often as four to six hours after the first exchange, and as I say, three exchanges usually do it.

I think that the use of ACTH has gotten us out of difficulties quite a few times. In babies who show extreme irritability, we begin the use of ACTH even before we have a single laboratory report.

Dr. B. H. Williams, Temple, Tex. Has the "heme pigment" been detected in the mother's serum before birth?

Is there hope that perhaps the determination of this pigment will give us a guide as to what to do? Should we interrupt pregnancy? If the changes that produce kernicterus are present, two or three weeks before the baby's birth, should one take the risk of prematurity in order to stop the pathologic process? Or, should we just wait? Do you think the determination of this pigment might be a better guide than the other tests we have had so far?

Dr. Felton. Dr. Abelson will not say it out loud yet, but in following these babies, the neurologic signs that we have discussed follow along with the appearance of this pathologic so-called "heme pigment" in the serum of the baby.* If you just look at our figures, our poor figures, I think you will see that prematurity must be avoided, that is, the added hazard of prematurity must be avoided at all costs in the management of erythroblastosis. Whatever the trigger is that sets this thing off and accelerates it so rapidly at the moment of delivery, we do not know, but it is accelerated or present in a much greater degree in any premature infant. We, therefore, would never recommend that a baby, or delivery of a baby be hastened before the actual time of delivery is announced. I think the determination of this "heme pigment" may not be the whole answer, and certainly we do not know what the trigger mechanism is, but I feel, as do some others, that this whole thing is connected somehow with deficient oxygen to the brain and has to do with the cross-over from fetal to adult type of oxygen.

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*This material has now been published.
Abelson, N. M., and Boggs, T. R., Jr.: Plasma Pigments in Erythroblastosis Fetalis. I. Spectrophotometric Absorption Pattern, Pediatrics 17:452, 1956; and Plasma Pigments in Erythroblastosis Fetalis. II. The Level of Heme Pigment; an Early Guide to Management of Erythroblastosis Fetalis, *ibid.* 17:461, 1956.

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The Use of Tetracycline in the Treatment of Acne Vulgaris:

A Clinical Study*

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Acne with the resultant scarring remains one of the major problems of the dermatologist. Antibiotics have proven to be a valuable adjunct in treatment in certain cases.

TETRACYCLINE IS A RECENTLY DEVELOPED ANTIBIOTIC produced by the catalytic hydrogenation of chlortetracycline[1] or by a fermentation process from a streptomyces, originally isolated from a sample of soil from Texas.[2] It differs only slightly in chemical structure from chlortetracyline and oxytetracycline. It is, however, more soluble, more stable in vitro, and produces fewer gastrointestinal symptoms than either of its two analogues.[3] All three are similar in their spectra of antibacterial activity. Differences in effectiveness against certain strains of gram-positive and gram-negative organisms do exist, however, and Welch has repeatedly stressed that equal activity should not be assigned to them just because of their close chemical relationship.[4, 5] When given in comparable doses, tetracycline gives higher levels in the serum, cerebrospinal fluid, and thyroid tissue than either of the other analogues.[6] It also diffuses readily in pleural and peritoneal fluids and is excreted at high levels in the milk of nursing mothers.[7] No reference could be found in the literature at hand that gave levels produced in the skin or in the secretions of sweat or sebaceous glands.

Clinical Study

In a previous paper we reported the results of treatment of 71 cases of pustular acne with orally administered tetracycline.[8] This report includes an additional 132 cases and is an attempt at objective clinical evaluation of the use of tetracycline in the management of the pustular forms of acne.

Approximately one-third of the patients were students in the University of Texas and were treated at the University Student Health Center. The remainder were patients seen in private practice. Only those individuals who had lesions with clinical evidence of infection were selected for treatment. The basis for this selection was the presence of papulopustules, pus and blood filled cystic lesions, or hard, painful, indurated nodules. All patients had previously received some form of conventional acne therapy but still presented therapeutic problems. In conjunction with tetracycline they were also treated with a drying lotion, placed on the usual dietary restrictions, and encouraged to cleanse their skin three times a day with soap and water. If marked oiliness of the skin was present, carbon dioxide snow was also used. Neither x-ray nor toxoid therapy was given. Each individual had a physical examination and, when indicated, blood counts and urinalysis were done. Attempts were made to correct such abnormalities as anemia, abnormal weight, or foci of infection. None of these patients had obviously infected tonsils or teeth.

Results

The results of treatment are summarized in tabular form (Table 1). Tetracycline was administered to 224 individuals with pustular acne. Of this number, 21 were lost from observation and are not included in the present study. The remaining 203 cases consisted of 93 males and 110 females. Their ages varied from 12 to 47 years with 80 per cent of the patients being under 22 years

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The tetracycline employed in this study was kindly supplied by the Upjohn Company, Kalamazoo, Michigan, whose trade name for tetracycline is Panmycin; and by Chas. Pfizer and Company, Inc., New York, whose trade name for tetracycline is Tetracyn.

TABLE 1

RESULTS OF TREATMENT

Dosage Schedule Mg. Per Day	*Complete Remission*	*Satisfactory But Partial Remission*	*Failure*	*Total*
100-300	12	67	—	79
500	15	81	—	96
750-1000	0	17	11	28
Total	27	165	11	203

of age. The duration of therapy ranged from 1 to 18 months with an average of 4.5 months per patient.

The clinical appearance of the individual as well as the patient's own opinion were used as criteria for evaluating the effectiveness of this treatment. Twenty-seven obtained complete remission. These individuals had disappearance of all pustular lesions. Only excessive oiliness or comedones remained. One hundred and sixty-five had partial but satisfactory improvement. These patients showed clearing of large pustules but still developed occasional indurated papules or very superficial pustules. Here again excessive skin oiliness and comedones required additional local therapy.

Eleven patients were classified as therapeutic failures. These individuals showed temporary improvement but had recurrence of numerous pustular lesions in spite of dosages up to 1 gram a day.

The only untoward side effect noted from the administration of tetracycline was a mild diarrhea in 7 individuals. Puritis ani, skin or mucous membrane lesions were not encountered. No abnormalities were found in complete blood counts done on 24 patients during the course of treatment. In no instance did we have to discontinue the medication.

The most difficult problem in this clinical study was the determination of a satisfactory dosage and the length of time this dosage should be administered. The schedules shown in the table represent the maximum daily amount given to the patients. In some instances, especially for those patients on 750 mg. per day, the amount was subsequently reduced to 500 mg. or less. That dosage which maintained control of the pustular element was the level considered most desirable.

The patients were seen at one to two week intervals. When evidence of infection had subsided, the medication was withheld. The majority had some degree of recurrence. Recurrence, however, was not often severe and did not occur until several weeks or months after the drug had been discontinued. Readministration of the same dosage again produced equal benefit. We did not find it necessary to give large initial or priming doses.

Comments

Despite the fact that local infection in the pilosebaceous apparatus and its importance as an etiologic factor in acne is still controversial, the use of antibiotics has been a great aid in the management of this disease. In the past five years the reports of Andrews,[9] Becker,[10] Robinson,[11] Noojin,[12] and others attest to their efficacy in the treatment of pustular acne. We agree with these workers that the established place of these drugs should be one of adjunct therapy for the control of the pustular phases of this disorder.

It has been our observation, and it coincides with that of others, that many individuals are nicely controlled with minimal dosage, i.e., one or two 100 mg. capsules per day. We have no adequate explanation for this occurrence. Perhaps it is due to a high level of diffusion or secretion into the pilosebaceous glands. Others have suggested it may be due to changes produced in gastrointestinal flora, or by action on internal foci of infection.[13] The emergence of clinically resistant pustular lesions has not been a problem. Patients who presented intermittent pustular flare-ups responded just as promptly each time short courses of the same dosage were given. The few failures reported, however, did not respond to this antibiotic. Several were changed to oxytetracycline with satisfactory response. In these instances the lesions possibly should have been cultured and antibiotic sensitivity tests made, as recently reported by Becker.[10] Miller[14] has pointed out, however, that organisms cultured from the acne pustule present many problems, and misinterpretation may account for the lack of parallelism between sensitivity tests and clinical response of the patient.

Many articles are appearing in medical and lay literature on the indiscriminate use of the various antibiotics. There seems to be no doubt that resistant strains of bacteria are appearing with increased frequency. This is especially true with so-called hospital infec-

tions. We are all aware of the serious staphylococcic enteritis and systemic moniliasis which may follow antibiotic administration. With no intention of minimizing these severe complications, we feel that they do not contraindicate the use of tetracycline as adjunct therapy in the management of pustular acne, especially in otherwise healthy individuals. The recent widespread interest in surgical planing of acne scars attests to the fact that these disfiguring lesions are of major concern to the patient. These sequelae are the result of our shortcomings in controlling the infection factor in this disorder. At present the broad spectrum antibiotics, preferably tetracycline, seem to be the best agent for prevention of scars. Actually these medications are the only new modality added to the treatment of acne within the past 20 years.

Conclusions

Tetracycline does not cure acne. It is, however, a valuable addition to the conventional forms of therapy. As determined from this clinical study, its value lies in the fact that:

1. It will entirely or partially control the pustular phases in most cases of acne.

2. Gastrointestinal symptoms or other side effects are almost negligible.

3. The emergence of clinically resistant pustular lesions is not frequent.

4. The average maintenance dose is 500 mg. per day. Some cases can be managed on smaller doses.

5. It is safe for long term (weeks or months) therapy.

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Discussion (Abstract)

Dr. Lee J. Alexander, Dallas, Tex. This study shows tetracycline to be a most effective adjunct to the management of acne vulgaris. A number of other investigators have come to similar conclusions. Schoch and I have used the antibiotics in the treatment of acne vulgaris for a number of years, and we are convinced that in some cases the antibiotic can be of indispensable value.

Discussions of this subject,—antibiotics in acne vulgaris,—invariably tend to precipitate two questions: (1) the indiscriminate use of antibiotics with the subsequent development of resistant strains of organisms; and (2) the prohibitive cost of this type of therapy. Indiscriminate use of the antibiotics certainly must be deplored (it would be ridiculous to think that all cases of acne should be treated with antibiotics), but this does not necessarily mean that the antibiotics cannot or should not be used intelligently in the treatment of acne vulgaris. This type of therapy is as important in a few well chosen cases of acne vulgaris as it is in other medical problems.

Relative to cost, satisfactory results can be obtained in the majority of cases at a cost to the patient which is not prohibitive, in fact, at a very moderate cost. Cost is dependent upon two factors, (1) size of the dose, and (2) duration of therapy. In a large majority of cases large doses of the antibiotic are not necessary. King and Forbes have shown this to be true in this study. Only 14 per cent of their patients received as much as 1,000 mg. of tetracycline per day, and in several of these patients it was possible to reduce the dosage to 500 mg. or less per day. There are certainly some cases of acne that will not respond satisfactorily to the smaller doses, or even to larger doses, of antibiotics, just as there are some cases that will not respond satisfactorily to other means of therapy. These are the "expensive cases" regardless of the method of treatment. It is in such cases we are called upon to exercise our dermatologic judgment (Schoch refers to this as "timing" of therapy). On the whole, however, of those patients with acne who are in need of antibiotic therapy most will respond to relatively small doses.

We find the antibiotics to be of value not only in cases similar to the ones described by King and Forbes, but also in those cases in which there is an exacerbation of the acne during the first few x-ray treatments. Our patients receive 250 to 500 mg. of

tetracycline per day for three to five days, and as improvement occurs the dosage is reduced (some patients will continue to do well on 250 mg. two or three times a week), and as soon as it seems prudent the antibiotic is discontinued. It is repeated if and when necessary. In some of those patients in whom tetracycline is not effective, erythromycin in correspondingly small doses frequently will be of immense value. In fact, in general it is difficult to decide which of these antibiotics, erythromycin or tetracycline, should receive first choice in the treatment of acne vulgaris. Many patients are benefited also by topical antibiotic therapy, namely, neomycin lotion with or without hydrocortisone, and frequently this seems to be as effective as oral antibiotic therapy. It is pleasant to use, it has good patient acceptance, and it is of particular value in the milder cases of acne vulgaris, cases which seem to be too mild to warrant oral antibiotic therapy.

This is not a plea to convert anyone to the use of antibiotics in acne vulgaris, nor is it a condemnation of any of the other measures used in the treatment of acne, but I do believe that in some well-selected cases the antibiotic has a definite place. It is a useful adjunct to the management of acne. It is not a cure.

Dr. S. S. Bowen, Houston, Tex. Dr. King and Dr. Forbes of Austin, Texas, have made an interesting study of a challenging disease, acne.

This study has been made of patients who are university students. Thus, these patients have been kept under good conditions of observation with adequate follow-up treatment, which results in an ideal field in which to study the therapeutic effects of various antibiotics. The selection of tetracycline is a tribute to this antibiotic, which apparently is the most effective in the armamentarium in the management of acne.

From the table it is apparent that the larger doses are not necessary. Results indicate that in a small dose schedule of 100 to 300 mg. per day, they were able to get complete remission in 12 of a total of 79 cases. In addition, 15 had complete remission with 500 mg. a day; and further observation of the table indicates that with larger doses of 750 to 1,000 mg. there was no complete remission in the remainder. These were the more severe cases, of course. In this large dosage group they had 11 failures out of 28 cases. Obviously the dosage varies in proportion to the degree of severity, with the probability of failure indicated in the more severe cases. This is in accordance with the general observation we have made, that some 15 per cent of acne patients were not benefited by any type of treatment.

The problem of the management of acne is essentially an individual one. Oftentimes simple cleanliness is all that is necessary. The clearing up of other foci of infection, such as removal of tonsils, or abscessed teeth certainly are necessary for cure. I agree with the authors that the side effects of antibiotics are minimal, and from the benefit we get from the administration of antibiotics, it is certainly worth both the cost and the minimal side effects that are sometimes encountered. In regard to diarrhea shown in some of the cases, it has been our experience that the capsules need to be taken with food. Of other interest is the sense of well-being that one experiences after taking tetracycline. The commentator can speak for this with authority in his own situation. After taking a course of tetracycline, the tremendously improved physical well-being is of considerable importance in a chronic situation such as this.

Further, we should be conscious of the possibilities of the use of sulfa drugs, as well as a trial of other antibiotics in the event of failure with one. This has been observed by all of those present. The failure one encounters in the 15 per cent of patients having the more severe forms of acne does not condemn the use of the drug. The need for repeated doses of this is certainly obvious. We all have had cases in which we get a temporary remission, and with adjunct therapy we are able to control the acne, only to have it come back again after a period of two to three months later. Subsequent treatment with the antibiotic previously successful, given usually with a small increase in dosage at first and working out a control smaller dose as benefits the individual in question, will again put the patient under control and increase the probability of eventual cure. From observation of a large number of cases I do not feel that they develop a sense of resistance to the antibiotic, since it is usually successful on retrial in the event of relapse of the acneform eruption.

In regard to the possibility of prevention of scars, the patients that need treatment with antibiotics are the ones that will have eventual scars; the use of antibiotics in preventing scarring in the severe acne is definitely indicated. I do agree with the authors that this type of therapy along with sulfa drugs has been the only thing that has been of a great value in the last twenty years in the treatment of acne.

Dr. William L. Dobes, Atlanta, Ga. I enjoyed Dr. King's paper because in many ways his experience parallels my own.

I think it wise to remember that antibiotics do not cure acne, but control pustulation and in this manner also help to prevent scarring. Unfortunately, recurrences are common unless other more effective measures are used to control the acne process itself.

In order to prevent recurrences of pustulation, I use, in conjunction with antibiotics, injections of a polyvalent staphylococcic vaccine in gradually increasing dosages. After experimenting with several brands, I have found Squibb's Staphylococcic *Ambo*toxoid most effective. This vaccine is phagelysed and incorporates both the exotoxic as well as the endotoxic principles of the organisms themselves.

I also have used in recurrent cases antibiotics, in minimal dosages, periodically over many months without having the patient develop a resistance to the drug. I do not believe that our in vitro and in vivo studies always coincide.

Dr. Hal E. Freeman, Springfield, Mo. The biggest disadvantage to this therapy, of course, is the cost. As you probably know, 250 mg. of an antibiotic cost about 40 cents and the 100 mg. do not cost proportionately less. I would not advise you to give 100 mg. because it costs not as much, but almost as much, as 250 mg.

I agree entirely with Dr. Bowen that you can give

250 mg. of some antibiotic for a while and then change to a sulfonamide in a maintenance dosage, which, at 0.5 gram, will cost you a nickel a tablet. You take eight of those a day and they would only cost you 40 cents; six or eight will serve you just as well as the antibiotic. That has to be considered by people who have to buy the medication.

Dr. Marcus Caro, Chicago, Ill. We treat acne vulgaris just about the same as everybody else does. We obtain temporary improvement and we have our recurrences just about the same as everybody else does. We talk a lot about the prevention of scars, but most of the patients we see are pretty badly scarred by the time we get them. One of our chief problems is convincing the patients that the x-ray treatment they have received has very little to do with the scarring they have.

My own personal experience has been that cryotherapy, which is being used less and less by most dermatologists, is in my hands still a very good adjunct to treatment. I still use it for all patients who have acne with scarring and I find that, added to the other treatments mentioned, cryotherapy does tend not only to improve the acne lesions but also the scarring. My experience also has been that the larger and more indurated the nodules, the larger the cysts and the more severe the acne, the more rapidly the patients improve. I have had many experiences, both at the clinic and at my office, of having patients whose acne was very repulsive, who after even one very strong cryotherapy treatment showed spectacular improvement within a week.

I should like to recommend that, in addition to all the other things you use, you add cryotherapy as a valuable adjunct both for preventing scars and for improving their appearance.

Beaumont's Description of the Gastric Juice

Pure gastric juice, when taken directly out of the stomach of a healthy adult, unmixed with any other fluid, save a portion of the mucus of the stomach with which it is most commonly, and perhaps always combined, is a clear, transparent fluid; inodorous; a little saltish; and very perceptibly acid. Its taste, when applied to the tongue, is similar to thin mucilaginous water, slightly acidulated with muriatic acid. It is readily diffusible in water, wine or spirits; slightly effervesces with alkalis; and is an effectual solvent of the *materia alimentaria*. It possesses the property of coagulating albumen, in an eminent degree; is powerfully antiseptic, checking the putrefaction of meat; and effectually restorative of healthy action, when applied to old, foetid sores, and foul ulcerating surfaces.

Saliva and mucus are sometimes abundantly mixed with the gastric juice. The mucus may be separated, by filtering the mixture through fine linen or muslin cambric. The gastric juice, and part of the saliva will pass through, while the mucus, and spumous or frothy part of the saliva, remains on the filter. When not separated by the filter, the mucus gives a ropiness to the fluid, that does not belong to the gastric juice, and soon falls to the bottom, in loose, white flocculi. Saliva imparts to the gastric juice, an azure tinge, and frothy appearance; and, when in large proportion, renders it foetid in a few days; whereas the pure gastric juice will keep for many months, without becoming foetid.

The gastric juice does not accumulate in the cavity of the stomach, until alimentary matter be received, and excite its vessels to discharge their contents, for the immediate purpose of digestion. It then begins to exude from its proper vessels, and increases in proportion to the quantity of aliment naturally required, and received. A definite proportion of aliment, only, can be perfectly digested in a given quantity of the fluid. From experiments on artificial digestion, it appears that the proportion of juice to the ingestae, is greater than is generally supposed. Its action on food is indicative of its chemical character. Like other chemical agents, it decomposes, or dissolves, and combines with, a fixed and definite quantity of matter, when its action ceases. When the juice becomes saturated, it refuses to dissolve more; and, if an excess of food have been taken, the residue remains in the stomach, or passes into the bowels, in a crude state, and frequently becomes a source of nervous irritation, pain and disease, for a long time; or until the *vis medicatrix naturae* restores the vessels of this viscus to their natural and healthy actions—either with or without the aid of medicine.

—William Beaumont, from *Experiments and Observations on Gastric Juice and the Physiology of Digestion*, 1833, pp. 84-86.

The Effects of Reserpine and Chlorpromazine on Orienting Behavior and Retention of Conditioned Reflexes*

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Interesting animal experimentation, employing reflex reactions, offers basic information regarding the effect of so-called tranquilizing drugs and may lead to their more rational use.

THE TWO CENTRAL NERVOUS SYSTEM DEPRESSANTS, reserpine and chlorpromazine have had unprecedented use during the relatively short time since their introduction. Unquestionably they have begun an era when more drugs of this nature will be used in the treatment of emotional illness. Though many investigations have reported the usefulness of these drugs, there is relatively little information on how they accomplish these beneficial effects. To shed more light on their mode of action, an experiment was designed to determine their effects on unlearned responses of dogs, and learned, conditioned responses in dogs. For this study unlearned responses are considered indicators of the animals' general reactivity. The conditioned responses are taken as indicators of the animals' learned reactivity. It is assumed that unlearned and learned reactivity are profitable ways to evaluate not only the functioning of normal organisms but those who are disturbed emotionally as well. For example, in human illness, phobic reactions, obsessive reactions and some types of anxiety reactions are thought to have their roots in early learned experiences and manifest themselves in the present when certain constellations of current stimuli trigger their release. In short, they seem to be based on learned associations even though these may be unconscious in nature. On the other hand, there also seem to be varieties of emotional illness which do not appear to develop primarily as a result of specifically learned responses but may be due to a failure to have learned appropriate reactions; to a breakdown of learned reactions in the face of overwhelming stress; and to secondary reactions to organic illness or to primary illness which is based on learning. In other words, the unlearned responsivity may be altered and constitute an important part of the disturbance. With such a general framework in mind, this study concerned itself with the effects of reserpine and chlorpromazine in the two situations just described.

Procedure

The experiment was divided into two parts, the first dealing with unlearned reactivity and the second with learned reactivity.

To assess the effects of these drugs on unlearned reactivity, the orienting response was employed. This is the sum total of an organism's reactions to a new stimulus and can be measured quantitatively. Pavlov[1] in 1910, first described this under the terms "orienting or focusing reflex" and later as "investigatory reflex." Others have referred to this as "questioning reaction"[2] and "vigilance."[3] Typically, the presentation of a new stimulus to a dog in an appropriate experimental situation elicits the following: (1) *increased motor activity* such as barking, pricking of ears, cocking the head back and forth, turning the body to the stimulus source, etc.; (2) *increased autonomic activity* such as accelerated cardiac and respiratory rates, glandular discharge, etc. These and other details of this behavior have been described by Robinson and Gantt.[2]

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As a rule, repeated presentation of the same stimulus, without relating it to something meaningful in the animal's response repertoire, usually leads to gradual weakening and final disappearance of the evoked orienting reactions. If a new tone of a specific frequency is regularly presented to an animal at intervals of two minutes, 10 to 20 times daily, the orienting response usually disappears in a week or 10 days. However, in some animals it may persist indefinitely. After a period of rest following the extinguishing of the orienting response it customarily will return. In general, the orienting response meets the criteria for being an unconditioned response. That is to say, it occurs in several species, is inborn and appears without training, and is present after ablation of the cortex. In the last instance repetition of the stimulus does not lead to extinction of the evoked reactions.

Five dogs, ranging from 3 to 7 years of age, 4 females and 1 male, were employed as experimental animals. Each had been trained to stand quietly and alone on a platform for approximately one hour at a time, in a closed, soundproof, experimental room. For each animal, before and after administration of the two drugs, motor orientation was measured on the basis of the strength of reaction to a 5 second exposure of a new stimulus. A single plus was used to signify a barely perceptible response; 4 plus an extremely strong response; and 2 plus and 3 plus as intermediate responses. The cardiac orienting response was selected as the indicator for autonomic orienting. An increase in heart rate to a 5 second exposure to a new stimulus compared to the heart rate in the 3 immediately preceding 5 second intervals was the criterion for cardiac orientation. To obtain this data two subcutaneous electrodes were placed in the animal under study and leads from these were fed into a constantly recording Brush electrocardiograph which was located outside the experimental room. The motor and cardiac orienting responses described have been used in this laboratory for the past 15 years. They are established phenomena which can be reliably reported.

The effect of a single relatively large dose of each drug on the motor and cardiac orientation of these animals was the procedure used. This was decided upon instead of daily continued maintenance doses for the following reasons: (1) the literature[4] and preliminary trials performed in this laboratory indicated that dogs are very sensitive to one of the drugs, reserpine; (2) the orienting responses could be expected to be extinguished within approximately 10 days. Thus, the experimental trials had to be completed well before this time.

On a given day, each animal was placed in the experimental room, given a parenteral injection of normal saline, and a control record made of the motor and cardiac orientation elicited by a 5 second exposure to a new stimulus (buzzer, bell or tone). This was presented once every minute for 10 trials. Thereafter, the test drug was administered parenterally. Following the lapse of an appropriate interval, the test trials were repeated in the same manner. When the drug had worn off, another series of trials were made to determine whether the orienting response had returned to pretest levels. This was necessary to distinguish between drug induced and extinction changes. The preliminary work with reserpine revealed that a dose of 100 μg. per Kg. produced a safe reduction of an animal's activity approximately 24 hours after administration and that this disappeared after about 72 hours. A comparable effect could be achieved with a 2.5 mg. per Kg. dose of chlorpromazine, but this was manifest approximately 2 hours after injection of the drug and disappeared completely after 24 hours. As a result, these dose levels were adopted for the test trials. In addition to the control trials, the reserpine effect was studied between 2 and 4 hours, 24 hours and 72 hours after administration. Chlorpromazine effect was studied 2 hours and 24 hours after administration.

The second part of this investigation was concerned with the effects of these two drugs on learned reactivity. The retention of a motor and autonomic conditioned reflex provided the means for studying this effect. Five dogs, which had been trained by classical avoidance conditioning procedures by the use of mild faradic shock as the unconditioned stimulus, were the experimental animals. The details of these methods used in this laboratory and their underlying philosophy are reported elsewhere.[5-9] The 3 female animals were used previously in the orienting studies and the 2 males were employed only for this

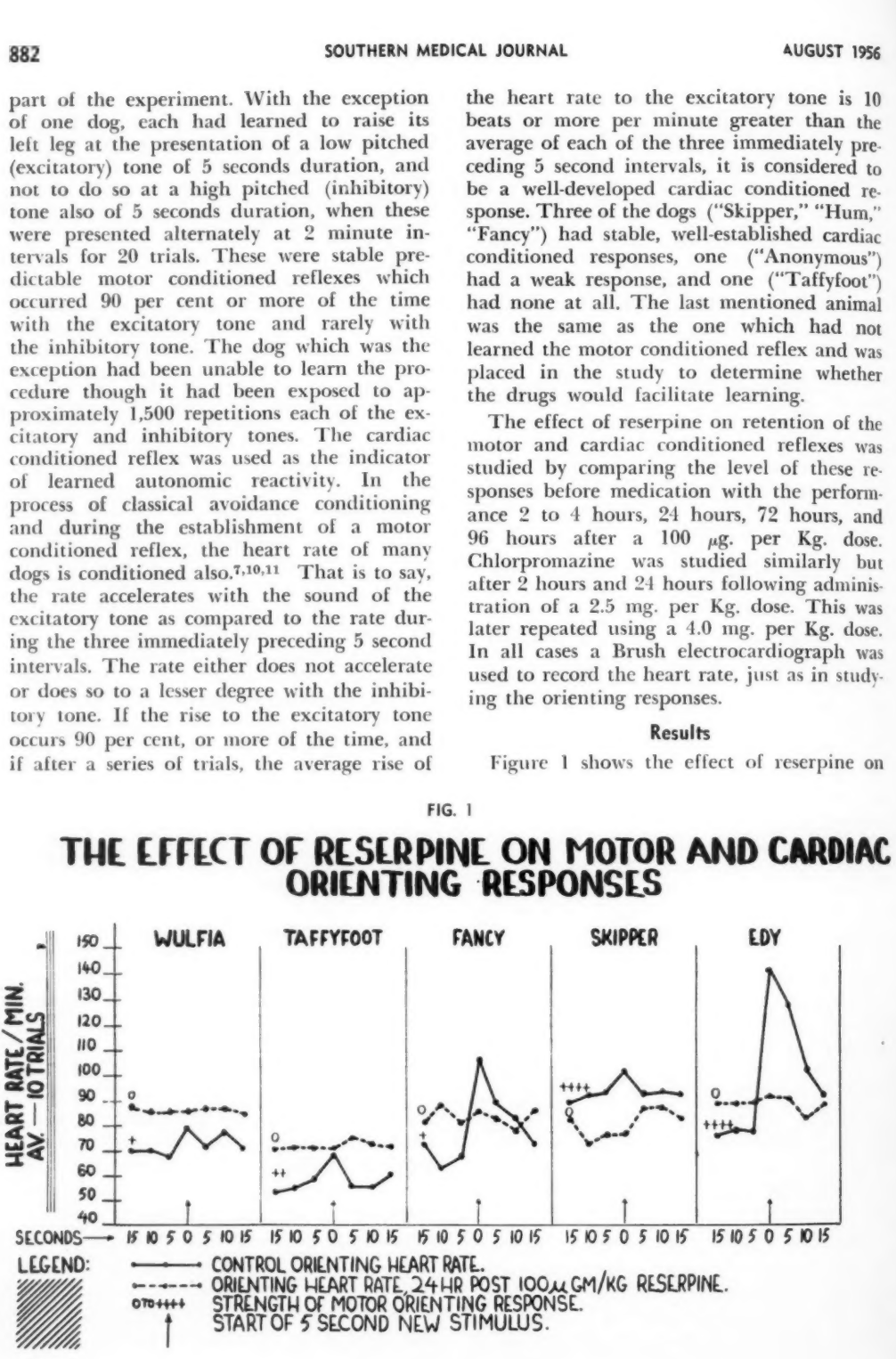
part of the experiment. With the exception of one dog, each had learned to raise its left leg at the presentation of a low pitched (excitatory) tone of 5 seconds duration, and not to do so at a high pitched (inhibitory) tone also of 5 seconds duration, when these were presented alternately at 2 minute intervals for 20 trials. These were stable predictable motor conditioned reflexes which occurred 90 per cent or more of the time with the excitatory tone and rarely with the inhibitory tone. The dog which was the exception had been unable to learn the procedure though it had been exposed to approximately 1,500 repetitions each of the excitatory and inhibitory tones. The cardiac conditioned reflex was used as the indicator of learned autonomic reactivity. In the process of classical avoidance conditioning and during the establishment of a motor conditioned reflex, the heart rate of many dogs is conditioned also.[7,10,11] That is to say, the rate accelerates with the sound of the excitatory tone as compared to the rate during the three immediately preceding 5 second intervals. The rate either does not accelerate or does so to a lesser degree with the inhibitory tone. If the rise to the excitatory tone occurs 90 per cent, or more of the time, and if after a series of trials, the average rise of the heart rate to the excitatory tone is 10 beats or more per minute greater than the average of each of the three immediately preceding 5 second intervals, it is considered to be a well-developed cardiac conditioned response. Three of the dogs ("Skipper," "Hum," "Fancy") had stable, well-established cardiac conditioned responses, one ("Anonymous") had a weak response, and one ("Taffyfoot") had none at all. The last mentioned animal was the same as the one which had not learned the motor conditioned reflex and was placed in the study to determine whether the drugs would facilitate learning.

The effect of reserpine on retention of the motor and cardiac conditioned reflexes was studied by comparing the level of these responses before medication with the performance 2 to 4 hours, 24 hours, 72 hours, and 96 hours after a 100 μg. per Kg. dose. Chlorpromazine was studied similarly but after 2 hours and 24 hours following administration of a 2.5 mg. per Kg. dose. This was later repeated using a 4.0 mg. per Kg. dose. In all cases a Brush electrocardiograph was used to record the heart rate, just as in studying the orienting responses.

Results

Figure 1 shows the effect of reserpine on

FIG. 1

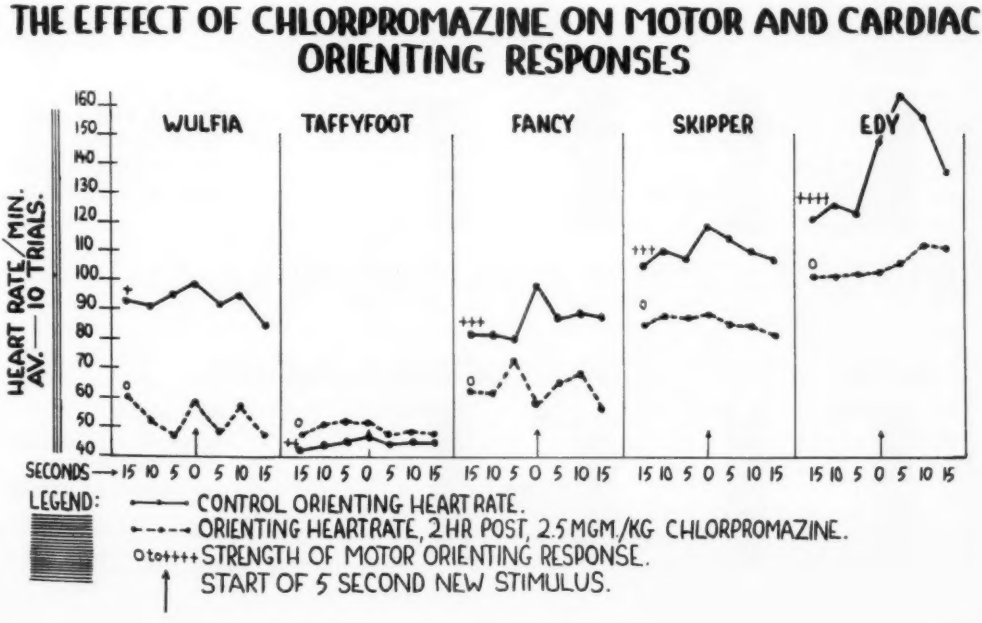


the orienting responses. Although there is no demonstrable effect of the drug between 2 to 4 hours following injection, at 24 hours the animals all showed the usual signs, i.e., miosis, relaxation of the nicitating membrance, diarrhea, occasional shivering, etc. Their activity was markedly reduced though they were able to walk and showed no gross neurologic damage. Compared to the barking and jumping about customarily associated with the entrance of visitors or workers, the laboratory was strangely quiet at all times. Likewise the activities of the animals when they were worked with or tended were changed. The usual playfulness and excitement upon being released from their paddocks disappeared. Instead, they remained in whatever position they were, until led to the experimental room. Then they quietly stretched out on the stand and showed no interest in the surroundings. When the new stimulus was presented to each of the dogs there was no motor orientation. The increased heart rate, which each of the animals previously showed to the new stimulus during the control period, also disappeared completely. While under the influence of the drug there was no difference between the heart rate elicited by the new stimulus and the three immediately preceding 5 second intervals. The plotted heart rate curve for the drug trial tended to be flat for each animal as compared to the control period where the curve always rose with the presentation of the new stimulus. The heart rate of the dog, "Edy," a hyperactive animal, almost doubled with the sounding of the new stimulus during the control period. When the animal was fully under the effect of reserpine, 24 hours after its administration, there was no rise with the presentation of the new stimulus, and the total heart rate curve was flat. It was found that this elimination of cardiac orienting occurred even though several of the animals showed an increase in heart rate while on reserpine. One dog, "Fancy," developed a transient cardiac arrhythmia while under the effect of the drug. Approximately 72 hours following the injection of the drug, all of the dogs returned to their premedication status with regard to motor and cardiac orientation as well as to general behavior.

Figure 2 shows the effect of chlorpromazine on the orienting responses.

The effects of chlorpromazine were noticed at approximately 2 hours after administration of the drug. The general behavior then was comparable in all respects to that ob-

FIG. 2



served with reserpine. Likewise there was no evidence of gross neurologic damage. However, such things as miosis, relaxation of the nictitating membrane, diarrhea, etc., were not present. The motor and cardiac orienting responses were completely eliminated. The heart rate curves of the control periods and while under the effect of the drug are comparable with those obtained with reserpine, except that chlorpromazine lowered the rate in all but one animal.

Figure 3 shows the effect of reserpine and chlorpromazine on the retention of motor conditioned reflexes. Both drugs markedly blocked the retention of these reactions, though it is clear that these were not completely eliminated. The dog "Anonymous," a lethargic, fearful animal whose behavior is easily disrupted by a variety of things, had a complete block in his retention of motor conditioned reflexes. There was a tendency for each of these drugs to impair slightly the capacity to differentiate between excitatory and inhibitory tones as indicated by the occasional lifting of the leg to the latter. "Taffyfoot," who never was able to establish stable, predictable conditioned reflexes, did not do so under the influence of these drugs.

Figure 4 describes the effect of reserpine on the retention of cardiac conditioned reflexes elicited by the excitatory tone. The cardiac conditioned reflex persisted, though dampened, in the dogs, "Skipper," "Hum" and "Anonymous." That is to say, following the presentation of the excitatory tone which signaled the imminence of a 1 second mild faradic shock in 5 seconds, the heart rate rose in spite of the medication. Before medication the rise in heart rate to the excitatory tone occurred in 100 per cent of the times for "Skipper," 90 per cent for "Hum," and 50 per cent for "Anonymous." Following the drug, this was reduced to 80 per cent for "Skipper," 80 per cent for "Hum," and increased to 70 per cent for "Anonymous." The dog "Fancy," who again developed a cardiac arrhythmia, showed no rise in heart rate to the excitatory tone on the basis of an average rate increase for the trials while under the effect of the drug. The arrhythmia consisted of irregular bursts of beats which heavily weighted the 5 second interval in

FIG. 3

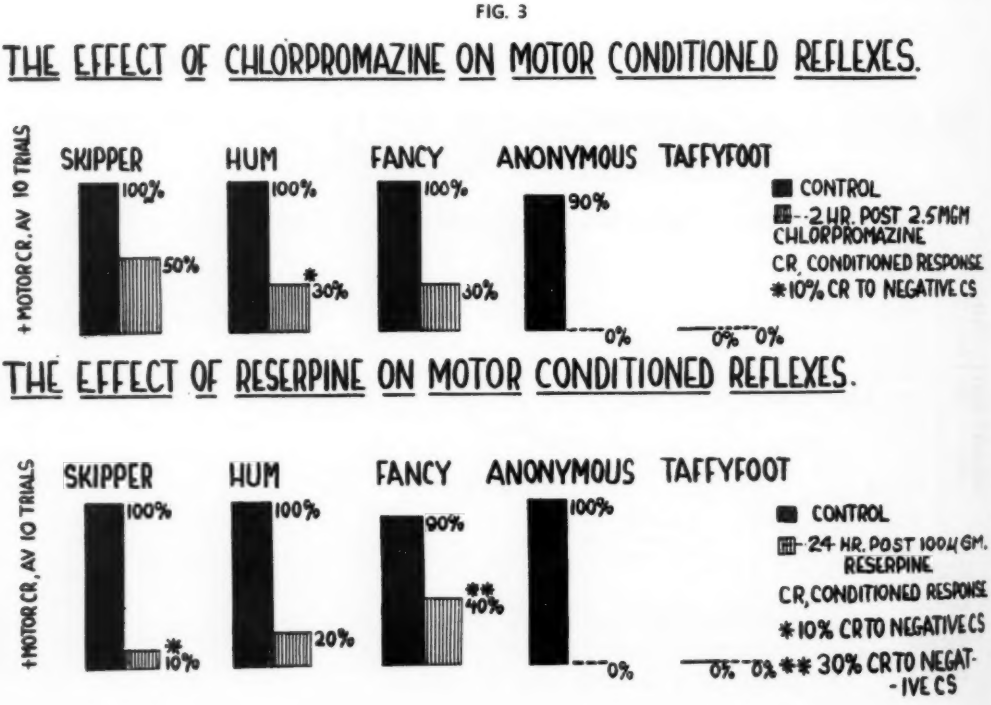
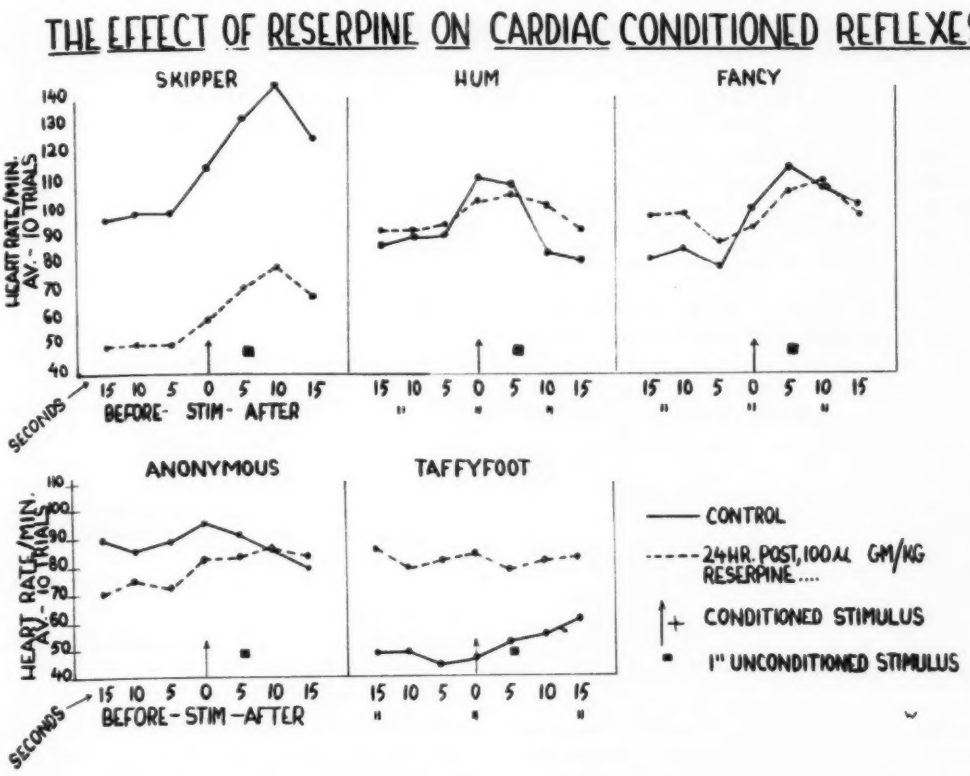


FIG. 4

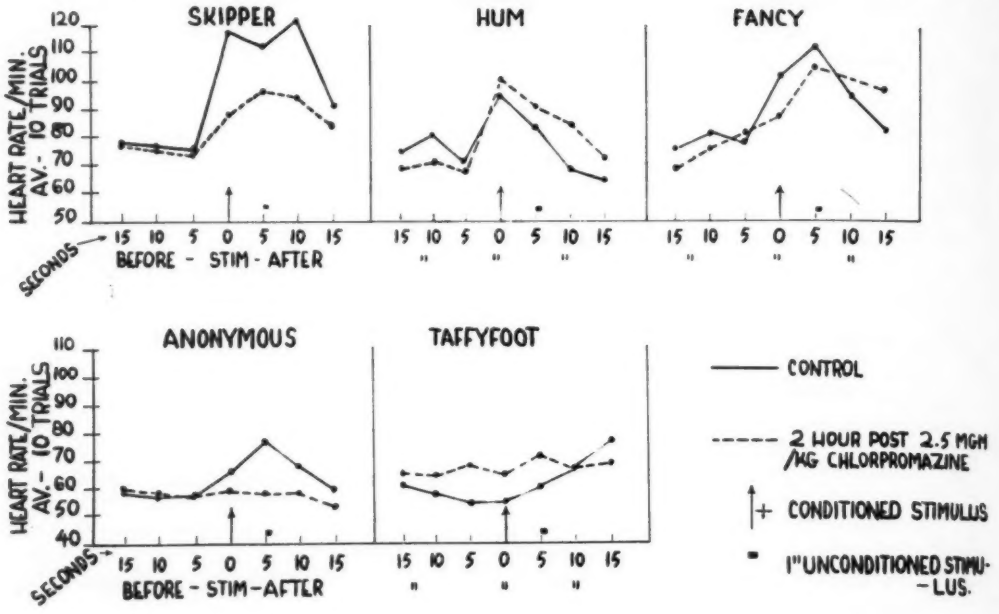


which they fell, and thereby greatly diminished the value of using the average of all trials as a criterion for the existence of a cardiac conditioned reflex. However, on the basis of the frequency of acceleration of the heart rate associated with the sounding of the excitatory tone, a cardiac conditioned reflex was present. This occurred 90 per cent of the time before drug and 50 per cent after the drug was given. "Taffyfoot" who did not have a conditioned cardiac reflex before treatment did not acquire one with reserpine. The slight effect of this drug on the cardiac conditioned reflexes is indicated also by the similarity between the shape of the heart rate curves in the control periods and the tests after the drug. The heart rate per se was not consistently altered though it tended to increase under the influence of this drug. The status as before medication returned in all animals after approximately 72 to 96 hours following the administration of reserpine, with both motor and cardiac conditioned reflexes returning at the same pace.

Figure 5 demonstrates the effect of chlorpromazine on cardiac conditioned reflexes. Here, too, the learned heart rate rise elicited by the excitatory tone which signals forthcoming shock persisted in three of the dogs. In addition, the heart rate curves of control and drug periods tend to have similar shapes. Prior to the trials with the drug, the rise in conditioned heart rate took place 100 per cent of the time in "Skipper," 100 per cent in "Fancy," 90 per cent in "Hum," and 70 per cent in "Anonymous." During the trials under the drug they occurred 80 per cent of the time in "Skipper," 100 per cent in "Fancy," 90 per cent in "Hum," and 45 per cent in "Anonymous." Only a slight arrhythmia was noticed in "Fancy" under chlorpromazine medication. "Taffyfoot" did not develop a conditioned cardiac reflex under this drug. In addition, the heart rate

FIG. 5

THE EFFECT OF CHLORPROMAZINE ON CARDIAC CONDITIONED REFLEXES.



tended to be slightly lower during the drug period than during the control trials as compared with reserpine. After 24 hours, all the animals returned to their premedication status, with motor and cardiac conditioned reflexes returning at about the same time. Four of the five animals were studied on a 4.0 mg. per Kg. dose with comparable results.

Discussion

For the dosage levels employed, this experiment reveals that reserpine and chlorpromazine have similar effects. These fall into a certain pattern. They completely obliterated motor and cardiac orienting responses, the indicators for unlearned motor and autonomic reactivity. Next, they interrupted to a moderate degree the retention of motor conditioned reflexes, the indicator for learned motor reactivity. Lastly, they blocked only slightly the retention of cardiac conditioned reflexes, the indicator for learned autonomic reactivity. In a sense this represents a profile of their potential usefulness. Assuming that symptoms and behaviors in psychiatric illness originate from altered unlearned (inborn) and learned patterns of behavior or combinations of each and that it is possible to classify them further by the degree of motor or autonomic involvement, these experiments may have clinical pertinence.

If one may be permitted to generalize from these studies, the greatest value of the drugs would appear to be in the reduction of nonspecific or unlearned motor and autonomic reactivity of organisms by insulating them from stimuli to which they are subjected but which do not have learned meanings. It would seem that these drugs might have their most value in those psychiatric illnesses in which excitement occurs because of breakdown of learned reactions due to overwhelming stress leaving as a residue heightened unlearned reactivity, or those in which there is overactivity due to failure to have learned appropriate responses, and where hyperactivity occurs as a result of secondary reactions to primary illness based on learning or as a result of secondary reactions to organic illness. Clinically, their success in excitement and panic states, generalized irritability, increasing the man-

ageability of restless, distractable, chronically ill patients who behave as if they have lowered thresholds of reactivity, in organically driven individuals including those with toxic states, and as adjuncts to electric shock treatment, are examples of this type of application. Their ability to impair the retention of learned motor activity endows them with further though limited use. Where the illness is such that its manifestation to some degree has been translated into the skeletal motor system, these drugs might interrupt such patterns. For example, aggressive urges of which the patient is aware, may be assumed to be a source of distress because of the danger of being carried out. That is to say, they already have major motor components. To the degree that this is so, these drugs may partially modify this state and increase the patient's comfort. Such conditions as tics, stuttering, and possibly certain obsessive motor acts may be modified partially. Obviously, the treatment is not through these drugs alone, for it is unlikely that the source of the illness would be altered. These drugs will be valuable here in facilitating psychotherapeutic approaches. Alone, it is conceivable they might even make the patient worse by disrupting the precarious stability achieved by formation of the symptoms.

Their least usefulness, on the basis of the previously cited reaction pattern, would appear to be in those illnesses where modification of learned autonomic reactivity is desired. Though the autonomic reactions typical of anxiety presumably can occur as the result of heightened but unlearned reactivity outlined previously and therefore be responsive to these drugs, anxiety which is based on faulty earlier learning would be ameliorated only slightly and unpredictably. It is assumed that other illnesses which may have arisen as a consequence of prior autonomic learning, such as phobic reactions, would fall in the latter category also.

The situation with regard to depressions is somewhat different. These drugs may decrease the reactivity of an already retarded patient. Or, they may expose a depression in a person, who is being sustained by the sheer impress of the stimuli present in his life situation, by the process of decreasing this source of support. One wonders whether this accounts for the depressions which have sometimes appeared in the course of treatment with these drugs. On the other hand, in conditions amenable to these drugs, secondary depression may be relieved to some degree by their use. By secondary depression is meant the state in which feelings of defeat and failure result from the repeated inadequate adjustment implied in being emotionally or organically ill.

Further data are needed to evaluate these drugs. It is necessary to know whether they prevent new learning. To do this, one will need to study the effect of the drugs on the acquisition of motor and autonomic conditioned reflexes. If a drug will block the retention of learning involved in an emotional disease, but will also prevent new learning, needed for a healthier readjustment to life as is implied in psychotherapy, its value will be limited. Thus far, two animals have been maintained under the complete influence of reserpine for several weeks, during which conditioning procedures were carried out. Though learning was delayed, both achieved partial motor and acceptable cardiac conditioned reflexes. No studies with chlorpromazine have been attempted as yet.

In any event, these studies do point out the value of using conditioning procedures as a means of determining the psychologic usefulness of drugs. They offer a method for establishing the pattern of a drug's potentiality which can augment other available information, and thus contribute to more rational use based on laboratory studies. From this type of approach it is felt that hypotheses can be drawn with regard to the types of behavior potentially susceptible to modification by a specific drug and permit their exploration through research. Experiments might then be designed for patients who exhibit these behaviors and the hypotheses be subjected to appropriate testing.

Summary

By means of conditioning procedures, the drugs reserpine and chlorpromazine were found to have similar actions. These actions were greatest on unlearned reactivity, both motor and autonomic. Moderate effects were found on the retention of learned motor reactivity. The least effect noted was on the retention of learned autonomic reactivity. The implications of these findings were related to clinical applications of these drugs.

The use of conditioning procedures to assess the effects of drugs on unlearned and learned reactivity as well as on the acquisition of new learning was stressed.

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Discussion (Abstract)

Dr. John E. Peters, Little Rock, Ark. Dr. Gliedman is to be complimented for his work with the CR-OR methodology which I know from my own experience is exceedingly difficult and tedious.

I would like to call attention to the long series of experiments, over a 25 year period, which have come from the Pavlovian Laboratory, directed by Dr. W. Horsley Gantt, at Johns Hopkins. Much of this work has dealt with the fundamental properties of the acquired behavior pattern (CR) and the underlying inborn behavior pattern, the OR. One is representative of predominantly cortical activity, and the other of predominantly diencephalic activity. Using these two indices or windows into the integrated functioning of the central nervous system, Dr. Gantt and his collaborators have investigated the effects of a host of drugs and physical agents and have contributed to our knowledge of these agents and of brain function. To name a few: alcohol, amphetamine, the barbiturates, other sedatives and hypnotics, anoxia, Adrenalin, acetylcholine, sulfanilamide, Metrazol convulsions, electrical convulsions, mescaline,—and now Dr. Gliedman's work on reserpine and chlorpromazine.

I would like to emphasize that many of these studies have shown that the temperament of the animal is an important factor in determining the pattern of the effect of various agents, and that the current state of the animal, whether he is "neurotic" or not, is important, and that his more immediate emotional state also influences results. For example, Dr. Gliedman's dog "Taffyfoot," which is an abnormal animal, ordinarily shows a very slow heartbeat, but both reserpine and chlorpromazine elevated the general level of her heart rate. "Skipper," on the other hand, an excitable dog, shows a generally decreased HR, as do many people, while under the effect of these drugs.

Robert A. Schneider, at the University of Oklahoma Medical School, found that reserpine had an effect on Central Sympathetic Reactivity (as measured by the Mecholyl-Funkenstein Test) that was dependent upon the characteristic pattern of the person before the drug was given. For example, in three persons with normal CSA, reserpine caused a decrease in CSA and in four persons with an already decreased CSA, reserpine caused an increased CSA. This bears a relation to the findings of clinicians that reserpine lowers an abnormally elevated blood pressure but does not have a proportionate effect on normal blood pressure.

The work of Renaldi and Himwich studying the effect of reserpine on the EEG patterns in animals bears a relation to Dr. Gliedman's findings, that is, they found no effect on the cortical EEG whereas there was an effect on the mesodiencephalic activating system. A difference in dosage and in the filtering of impulses through complex processes to peripheral activity could account for the apparent difference in interpretation.

Dr. Gliedman raises the question as to whether these new drugs might facilitate psychotherapy. In correlating this idea with the laboratory investigations of CR, I think the results will depend very much on: (a) the dosage employed; (b) the duration of treatment; (c) the temperament of the animal; (d) whether or not the animal is behaviorly pathological; and (e) whether a clear-cut differentiation can be maintained, in the design of the experiment, between more purely intellectual learning and the more purely emotionally or autonomically toned learning.

Ideally we are looking for drugs which help an animal to release an old learned pattern and to take on a new pattern. Dr. Gliedman has made a contribution in this direction. I wish to express my appreciation to him for the opportunity to comment on his research.

Dr. B. H. Williams, Temple, Tex. Dr. Gliedman, I should like to ask your opinion with regard to the administration of chlorpromazine and also reserpine to small children and infants. As you probably know, reserpine has been advocated for the irritable and hypertonic infant as reported at the New York Academy of Sciences last February. I think it is probably being widely used not only as a short-time medication, but also as a "day-in-day-out" medication in some instances.

In view of your experimental work just described, do you believe there is any justification for the administration of either chlorpromazine or reserpine to the infant who may be vomiting symptomatically from one of many different causes, or to the infant who may be hyperreactive from one of many different reasons?

Dr. Gliedman (Closing). I am sorry that I cannot answer the question you raise. The animals I used in the laboratory were all full grown so I am

unable to offer you any comparable situation there, and I have no clinical experience that directly relates to the problems you have raised. However, it is my own feeling that extreme caution is necessary when using these drugs on very young, growing organisms. A colleague of mine has successfully employed reserpine for the control of stuttering in children and without any deleterious effects. Incidentally, before he told me of this, he asked if the experimental work that Dr. Gantt and I were doing suggested that this drug might have potential value in the treatment of this type of speech disorder. Since reserpine and chlorpromazine both partially interrupted learned motor conditioned reflexes, I ventured the opinion that either of them might be helpful and was gratified to find that reserpine did help considerably. There are many reports in the literature relating to the safe use of these agents for a variety of conditions in the age group about which you are concerned. As you know, these are powerful drugs and their effects, especially from prolonged usage in the younger growing organisms, are incompletely known. I would try other things first and then resort to these agents.

I believe that studying drugs in the way suggested will enable us to obtain a pattern of their usefulness. By means of animal studies, one can obtain leads from which to design experiments to study specific drug effects on similar human behaviors regardless of diagnostic category. Psychiatric diagnoses are at best very limited, being descriptive and variable. It is my opinion that this approach might avoid some of the pitfalls inherent in the procedure which employs a drug either for all patients of one diagnostic category or for all patients, regardless of diagnosis, who happen to be residents of a certain ward or wards of a hospital.

I would like to mention that Dr. Peters' point about the importance of the temperament of an animal is a very important one. Because of the time limitation, I was unable to elaborate this. The animals used in this study ran the gamut of the Pavlovian types but nevertheless, the effects of reserpine and chlorpromazine are apparent.

Sydenham on Gout

1. Either men will think that the nature of gout is wholly mysterious and incomprehensible, or that a man like myself, who has suffered from it thirty-four years, must be of a slow and sluggish disposition not to have discovered something respecting the nature and treatment of a disease so peculiarly his own. Be this as it may, I will give a *bona fide* account of what I know. The difficulties and refinements relating to the disease itself, and the method of its cure, I will leave for Time, the guide to truth, to clear up and explain.

2. Gout attacks such old men as, after passing the best part of their life in ease and comfort, indulging freely in high living, wine, and other generous drinks, at length, from inactivity, the usual attendant of advanced life, have left off altogether the bodily exercises of their youth. Such men have generally large heads, are of a full, humid, and lax habit, and possess a luxurious and vigorous constitution, with excellent vital stamina.

3. Not that gout attacks these only. Sometimes it invades the spare and thin. Sometimes it will not wait for the advance of age. Sometimes even the prime of life is liable to it. This happens most where there is an unhappy hereditary tendency; or, even where (without such being the case) the patient has overindulged in premature venery. The omission, too, of any customary violent exercise brings it on. So, also, does the sudden change from over-hearty diet in the way of meats and drinks, to a low regimen and thin potations.

4. When it attacks a person worn out by old age, it is neither so severe as it is when it takes hold of a young man, nor has it such stated periods. They say it is because generally life passes away before it comes to a climax, and also because the native heat and vigour of the body being diminished, it breaks out upon the joints both less regularly and less vehemently. But if it attacks any person late in life, although it neither fix upon its seat so regularly, nor handle him so severely, it still takes its ground by degrees, so as to lay down a law for itself and choose a type. This it does both in respect to the time of the year in which it intends to open the campaign, and in respect to the duration of the fit. Uncertain as are its periods, slight as may be the torture for a few days, irregular as may be its invasion and retreat, it is still gout, and its later attacks are worse than its earlier.

—From *The Works of Thomas Sydenham*, Vol. II, p. 123. Translated by R. G. Latham. (Thomas Sydenham, 1624-1689).

Recurring Acute Respiratory Infections in Children*

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The allergic child presents an especial problem in the matter of recurrent upper respiratory infections. The author outlines the factors in etiology and management.

THE TYPICAL CHILD WITH RECURRING ACUTE RESPIRATORY INFECTIONS is usually of preschool age.[1] He has a respiratory infection about once a month. It usually begins as a common cold. Secondary bacterial infection results in a spread to the adjacent structures: ears, sinuses, cervical nodes, tonsils or lower respiratory tract. It may be complicated by allergic rhinitis or asthma. There is often high fever at the onset which leads to treatment with some antimicrobial agent. The fever usually subsides quickly but the symptoms disappear slowly over the next 7 to 10 days. The child is well for one or two weeks and then the whole cycle commences again. The infections begin with the first colds in September and continue into April or May.

The increasing number of antimicrobial agents has not always helped the physician in treating the child with recurring acute respiratory infections. Rather it has resulted at times in the blind prescription of one drug after another. This in turn creates additional problems such as: drug or hypersensitivity reactions, masking of the disease process, the origin of new strains of bacteria, or the development of resistant strains. The solution of the problem of recurring respiratory infections is therefore not the administration of one antimicrobial drug after another. Good management will result only if the underlying etiologic factors are discovered, a point recently stressed by the otolaryngologist, Sanders.[2] It is the purpose of this paper to present methods of diagnosing and treating children with recurring acute respiratory infections. Illustrative case histories are appended.

The well-known instruments of a careful painstaking history and physical examination are used with the necessary laboratory studies. Long-term observation may be required to reveal some of the underlying causes.

The History

In the *family history* there are two aspects to be considered. The most important is to determine the presence of a "healthy carrier" in the home, (parents, siblings, boarders, servants, grandparents). Kempe[3] has pointed out very forcefully that the "healthy carrier" may act as a reservoir of infection in the family. He showed in a number of cases that the child with recurring infections could only be helped by clearing up the carrier. Secondly, a positive family history of allergy suggests that the child may be allergic.

The *past history* may reveal allergic symptoms of the gastrointestinal, cutaneous or respiratory systems. In addition such aspects of the child's life as his diet, sleep, habits of elimination, growth, development and schooling are thoroughly reviewed.

The *present history* will attempt to unearth allergic respiratory symptoms of a seasonal or perennial nature. The persistence of cough, nasal discharge or irritation helped by antiallergic measures, and made worse with pollen, house dust, animal danders would suggest allergy. The temporal relationship between the child's infection and that of other members of the family is recorded. Is there improvement with antibacterial drugs, gamma globulin, respiratory vaccine or the warm summer months?

Physical Examination

Physical examination of a child with recurring acute respiratory infections does not always show him to be thin, "washed-out," pasty looking, and of fine bones. At times his

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nutrition, growth and development may be excellent. But as one observes this child the long-erm effect of bad health reveals itself in a poorly nourished, tired child with delayed growth and maturation. In children who are allergic the complexion is often sallow. They appear to be anemic but the hemoglobin is well within normal limits. The facies, often pinched with protruding upper incisors producing a "Bugs Bunny" appearance, is due to chronic nasal obstruction which results in a high arched palate and broadening of the maxilla. The tympanic membranes may show thickening with considerable retraction or there may be fluid behind the eardrums. Hearing is often decreased. The latter condition, termed secretory otitis media, is considered by otolaryngologists to be due to allergy, chronic sinusitis or chronic adenoiditis.

The eyes may show blepharitis, vernal conjunctivitis or chronic infection of the conjunctiva with occasional small hemorrhages due to severe paroxysmal cough. The nasal mucous membrane in uncomplicated allergy is pale, slate gray, glistening, edematous with fine strands of mucus running across from the inferior turbinate to the medial wall. There may be a watery mucoid discharge. At times the mucous membrane in an allergic child appears normal. However, with the advent of infection the mucous membrane becomes red, swollen and the discharge is mucoid or muco purulent. The underlying allergic rhinitis is covered and only when the infection clears does the true picture become apparent. The pharynx is often red with rather marked hyperplasia of the lymphoid tissue in infection and pale or slightly pink in uncomplicated allergy. If the infection progresses the pharyngeal wall has strands of connective tissue running through the lymphoid tissue producing the cobblestone or granular pharyngitis. This is usually covered with a gray white exudate, the postnasal drip, that causes the persistent coughing, gagging and vomiting and the raw dry throat. The tonsils may be small or large. As a rule there are enlarged anterior and posterior cervical nodes extending along the sternocleidomastoid to the clavicle. The chest wall is usually normal in appearance except in those children with chronic asthma. Auscultation may be within normal limits or one may hear wheezes, squeaking rales or rhonchi.

The regrowth of the tonsils and adenoids following tonsillectomy and adenoidectomy is often seen in the allergic child.[4] The presence of the persistently enlarged cervical nodes, chronically infected tonsils, granular pharyngitis, purulent nasal discharge denote a focus of infection that may require the assistance of an otolaryngologist and subsequent operation.

Laboratory Studies

Laboratory investigation is not done routinely. It is only used to assist in making a diagnosis. X-ray examinations may demonstrate sinusitis, excessive lymphoid tissue in the nasopharynx, and in the chest enlarged lymph nodes, foreign body, atelectasis or chronic pulmonary disease. Occasionally bronchoscopy with lipiodol studies are indicated. Nasal smears may be necessary in differentiating between allergic rhinitis and infection, since inspection alone may be very misleading. Nose and throat cultures with sensitivity tests of the organisms are valuable in difficult cases. Blood counts may assist in differentiating between infection and allergy. Eosinophils are sometimes found only in the acute allergic episode. Studies to rule out tuberculosis, histoplasmosis, coccidioidomycosis, and cystic fibrosis of the pancreas are done when necessary.

Management

The management of recurring acute respiratory infections in children depends upon the etiologic factors that are elicited. Since allergy may play such an important role every effort must be made to control it. Most failures are due to either not recognizing it or disregarding it. A few of the more salient features for allergic management will be touched upon. Inhalants and foods are the chief offenders with the former causing many of the difficulties. In the inhalant group dust and molds give the most trouble. Occasionally animal danders, wool, cotton, and pollen may cause considerable respiratory allergy. The use of a dust and mold free bedroom will often afford considerable relief. An electrostatic air cleaner frees the room of most obnoxious inhalants. An electric or gas heater is cleaner than a floor furnace or forced hot air. With the onset of cold weather the bedroom windows should be closed. The humidity is best maintained around 40 to 50 per cent

with a vaporizer. Many children watch television while lying on a rug. The rugs and over-stuffed furniture in the TV room should be sprayed with Allergex or Dust Seal which quite effectively control mold and dust.

Elimination of food does not produce results very often, only in about 10 per cent of the patients in our experience. However, it is simple and worthy of trial since its effects may often be quite spectacular. Whenever it is feasible removal of foods during an infection-free period may be tried for four days. The foods I have found to be the most troublesome are chocolate, wheat, spices, milk, fish and corn. It is recognized of course that any food may cause difficulties. A new food is added every four days to determine its effect. Some children will require further allergic studies with skin tests and desensitization. For further details in allergic management the reader is referred to Ratner,[5] Dees,[6] and Halpern.[7]

The so-called nonspecific factors may be very important in bringing on colds. And while it is recognized that most colds are viral in origin they are of significance because they produce changes in the pH of the mucous membranes that allow pathogenic bacteria to multiply rapidly.[8,9] Chilling is the most important of the nonspecific factors in recurring acute respiratory infections. Susceptible children need to wear a shirt and undershirt. A T-shirt is bad for them because it becomes wet with sweat and then may chill them. In cold weather the children should wear overalls or blue jeans. As the days become shorter they are brought indoors before it becomes damp and cold. They should be bathed only when necessary and then be protected from chilling. In the summer they are allowed to go swimming but they are covered immediately after coming out of the water. Room temperature is maintained between 68 and 72 degrees.

The problem of the child between 3 and 6 years is often caused by the nursery school. There are children who are not mentally or psychologically ready for the first grade, and similarly there are children who are not physiologically ready for nursery school. That is to say their level of immunity or natural resistance is so low that each time they are exposed to a child with a cold they become quite ill with otitis, cervical adenitis, bronchitis, etc. Their parents are so alarmed that they deluge the pediatricians with requests for vitamins, tonics, "cold shots" and iron. The solution is often very simple, namely removal of the child from school. I have suggested to parents who feel that their child needs nursery school to go through the neighborhood and find three to five other children who do not attend nursery school. Each parent takes the group for one morning a week. A curriculum is set up. It teaches the parent much in the way of handling a group. Infections are markedly reduced in number because a mother will not send a child with a respiratory infection to a small group. Often the child can attend nursery school the following year without difficulty.

Diet may be a factor that needs more study in the prevention of respiratory infection. Powdered skim milk is a very valuable means of adding more calcium. Natural vitamins, especially C, are worthy of trial. Recent publications have noted the value of the citrus flavonoids in respiratory infection.[10] Dean[11] states "a proper diet is such an important factor in the prophylaxis of nasal sinus disease and in the treatment of nasal sinus infections." He feels that sleep, rest and play are important too but that with improvement in food habits alone nasal and ear infections have improved.

Antihistamines alone or combined with ephedrine may be very helpful in aborting colds that are probably allergic in nature. This seems to me to be important because if the allergic manifestations are controlled secondary bacterial invaders are less likely to get a foothold.

It is very tempting to enter into a long discussion apropos of bacterial allergy and the value of respiratory vaccine.[12-15] This would not serve any useful purpose here. It is still a much debated subject. Suffice it to say that good results are often obtained by either stock or autogenous vaccine. It is difficult to get a good autogenous vaccine. The success of vaccine treatment often is determined by the method of administration. Usually it is given in doses that are too small. Vaccine treatment is best begun in the nonrespiratory season. Some clinicians do an intradermal test to determine the first dose. This has not been very helpful to me. The first dose is 0.05 cc. of the undiluted vaccine and it is increased by

0.05 cc. every 4 to 7 days until the optimal dose for the individual child is reached. This amount is an empirical one. It is predicated on whether there is a local or systemic reaction. If either of these occur the dose is not increased. The injections are then given every 2, 3 or 4 weeks. Four weeks seems to be the maximum time the child can go between injections. The injections are given deep subcutaneously.

If the respiratory season has begun and the individual has a respiratory infection he is usually in a hypersensitive stage. The vaccine is diluted 1:100 or 1:1,000. Small doses are given carefully. At times it may be wise to give an antimicrobial drug along with the respiratory vaccine. This allows one to increase the dose of the vaccine more quickly and safely. I have gone into much detail about the administration of vaccine because I believe that many failures are due to the method of administration. Vaccine may not be effective if the allergic component is disregarded or if necessary surgery of the tonsils and adenoids is not performed. There may be some who will claim that the vaccines effect is a nonspecific one. Perhaps this is so but there are children who get excellent results with vaccine.

When a vaccine cannot be used, or is unsuccessful an antimicrobial agent in small doses may effectively keep the child free of recurring respiratory infection. This has been noted by Shuey and Grater.[16] Sulfadiazine in doses of gr. v to viiss twice daily is the drug of choice because it is cheap, well tolerated and works well. Gamma globulin may be successful when other measures fail. It is given every 6 weeks in doses of 0.2 cc. to 0.3 cc. per pound of body weight.[17] Bowen [18] reported a large series of cases with favorable results.

Recurring respiratory infections may be due to inadequate or incorrect antimicrobial therapy or to a deep seated walled off infection in the sinuses, tonsils, adenoids or cervical nodes. In the latter instances results will be excellent if the necessary otolaryngological procedures are performed. There will be regrowth of lymphoid tissue in the nasopharynx and tonsil areas if allergy is overlooked.[4] Most otolaryngologists and allergists are agreed that the allergy should be treated first. Often this will obviate the need for surgical treatment. The indications for operation in allergic children are the same as those for nonallergic ones, namely, marked hypertrophy, recurrent infections and otitis media.

The presence of a "healthy" individual in the child's environment may be the sole cause of the recurring acute respiratory infections. This person may be a mother with "chronic sinus," a grandmother with chronic bronchitis, or an older sibling who attends school and has frequent colds. When the infection is eliminated from these people the child becomes well. In some instances we have had to treat the entire family with vaccine or sulfadiazine prophylactically before successfully controlling the child's infection. This fact is overlooked too often in spite of the evidence presented by Kempe.[3] However, in defense of parents one might cite the three year study of 1,100 families made by Coulter and Tucker.[19] They showed that young children with their high incidence of acute respiratory illness present a greater risk of illness to their parents than do older children. Thus it often becomes necessary to treat the entire family in order to help the child with recurring acute respiratory infections.

Summary

The successful treatment of recurring acute respiratory infections requires a painstaking study for the underlying etiologic factors by means of the history, physical examinations, laboratory studies and observation of the patient. Control of these factors is achieved by such procedures as: (1) allergic management, (2) treatment of the "healthy carrier" in the family, (3) removal from nursery school, (4) improvement of diet, (5) indicated surgery, (6) prevention of chilling, (7) respiratory vaccine, (8) gamma globulin, and (9) the proper use of antimicrobial agents prophylactically and therapeutically.

Case Reviews

Case 1. (Probable bacterial allergy helped by surgery.)

C. M., a 5 five year old girl, was a mouth-breather because of greatly enlarged and chronically infected tonsils and adenoids. She had many episodes of tonsillitis, cervical adenoiditis and otitis. At times she had considerable allergic rhinitis without apparent infection which was relieved by antihistaminics. Elimination of certain foods was of no value. Nasal smears taken during an infection-free period when the nasal mucous membranes were pale showed neutrophils 3 plus, eosinophils 1 plus. Tonsillectomy and adenoidec-

tomy was performed and since then there has been no evidence of allergic rhinitis. There was no *past history* for cutaneous or gastrointestinal allergy. The mother has hay fever.

Case 2. (Asthma with infection helped by allergic management without the need of surgery.)

J. M., a 5 year old boy, had asthma since the age of 18 months. It was present the year around and was always accompanied by high fever and frequent attacks of tonsillitis. He was advised by many physicians to have an operation. Past and family histories were negative. Skin tests in our Allergy Clinic revealed positive reactions to: dust, tree pollens, danders and some foods. Treatment consisted of food elimination and dust desensitization. After the first month of treatment he had no asthma. One attack of tonsillitis and otitis, and several episodes of nasopharyngitis occurred without asthma. The tonsils have receded in size and it now appears that tonsillectomy and adenoidectomy will not be necessary.

Case 3. (Asthma and allergic rhinitis not helped with antibiotics, steroid therapy, allergic management, or prophylactic antibiotics until surgery was done.)

J. S., age four and a half years, had asthma accompanied by severe respiratory infection since the age of one year. He had been hospitalized elsewhere 12 times. Treatment consisted of antibiotics, steroid therapy, epinephrine, and aminophyllin. Symptoms persisted in spite of the use of prophylactic antibiotics. Allergy studies revealed positive skin tests to dust, molds, and ragweed. Desensitization alone did not help, nor did desensitization with antibiotics to which was later added respiratory vaccine. Tonsillectomy and adenoidectomy were done 18 months ago. Since that time he has done very well with anti-allergic desensitization and added vaccine. Occasionally he wheezes but has had several respiratory infections without asthma. There is much allergy in the mother and siblings.

Case 4. (Asthma and allergic rhinitis not responding to vaccine alone, to vaccine and anti-allergic desensitization, nor tonsillectomy and adenoidectomy, but to gamma globulin.)

T. P., age 6 years, was very allergic since early infancy. He had gastrointestinal and respiratory allergy. Since age one year he has been observed in the Allergy Clinic where skin tests on several occasions showed positive reactions to the inhalants, (dust, molds and grass). Results were only fair with vaccine and allergic desensitization measures, operation, and prophylactic antibiotics, but with the addition of gamma globulin he has done exceptionally well. He had a normal value from gamma globulin and a negative Schick test. The mother has hay fever.

Cases 5, 6, and 7 demonstrate various aspects of the "healthy carrier" in the family acting as a reservoir of infection.

Case 5. C. F., a 2 year old boy, had frequent attacks of nasopharyngitis, otitis media, bronchitis and asthma since his birth. He cried a lot. Orange juice and oleum percomorphum caused gastrointestinal upsets. The child was an adopted one. The mother and father worked and the grandmother cared for child. She had a chronic cough with expectoration of purulent material. At 10 months of age the mother stopped work and cared for the child in her own home. Since then the child has had occasional colds but has required no antimicrobial therapy over the past 12 months.

Case 6. P. W. family, mother and three children aged 9, 7 and 4 years had one acute respiratory infection after another. Infection would begin with one child, spread to others and then the mother would become ill. She would then infect one of the children and the cycle would begin again. During the middle of the second winter the entire family was placed on sulfadiazine in small doses twice daily. There were no illnesses the remainder of the winter. The third winter occasional infections were present in the younger child. Last winter the family did well without any specific treatment. The father has allergic rhinitis.

Case 7. H. R. The mother has had chronic sinusitis that required frequent visits to an otolaryngologist for many years. The two children had numerous episodes of nasopharyngitis, otitis, cervical adenitis, and bronchitis each winter. An autogenous vaccine was made up for the mother and two children. Maximum dose has been 0.8 cc. every 4 weeks. They have been under treatment for 18 months. The mother and children ages 7 and 5 have been well, and the mother has not visited an otolaryngologist since the treatment was begun. The family history is negative for allergy.

Cases 8 and 9 illustrate the effect of removal from nursery school in an allergic and nonallergic child.

Case 8. C. Z., age 5 years, had numerous attacks of otitis, bronchitis and tonsillitis; she has mild allergic rhinitis. At age three and a half years she was removed from nursery school and did well the rest of the year. The following year she entered nursery school and had a few respiratory infections. The mother has hay fever and hives, the father hay fever.

Case 9. G. S., age 18 years, had numerous respiratory infections during her third and fourth year of life which were only controlled by removal from nursery school. Since age 5 years she has been extremely well. The mother has hay fever, hives and angioneurotic edema.

Case 10. (Effect of respiratory vaccine in a nonallergic child.)

J. L., age 8 years, had purulent nasal discharge associated with otitis media, sinusitis and fever each year since three and a half years of age. The symptoms began in October and did not disappear until April; in the warm months he was quite well. Treatment had consisted of antibiotics by his pediatrician. If these did not successfully control infection he was sent to an otolaryngologist who washed out the sinuses. Each episode lasted two or three weeks and there were five or six each year. Tonsillectomy and adenoidectomy at 5 years was without much relief. The past history revealed no allergic disease of the gastrointestinal, respiratory or dermal systems. (The mother had hay fever.) Nasal smear showed no eosinophils, many neutrophils, and few bacteria. The nasal mucous membrane was red, boggy with purulent exudate. The

pharynx was red, and granular with considerable hyperplasia of lymphoid tissue.

An autogenous vaccine was made up that contained beta hemolytic streptococci, gamma streptococci, and Staphylococcus aureus. Treatment was begun on November 3, 1953. He had fever and profuse purulent nasal discharge following the first injection in spite of the small dose used. The vaccine was further diluted and he was placed on Terramycin. By November 12 he was much improved. In the next 22 months he had occasional episodes of nasopharyngitis. None of these were accompanied by fever and he recovered without any specific treatment. It was the first time in 5 years that he went through a respiratory season without antibiotics or visits to the nose and throat department. The maximum dose was 0.7 cc. which was given every 4 weeks. He gained ten and a half pounds in weight, and four inches in height during this time. His mother was very reluctant to stop treatment.

Case 11. (Effect of prophylactic sulfadiazine in a nonallergic child.)

P. M., a three and a half year old boy, had frequent severe respiratory infections of the upper and lower respiratory tract. He was hospitalized three times. At two and a fourth years he was placed on prophylactic sulfadiazine. He has been very well except for one attack of tonsillitis that occurred when the mother omitted drug. The family history was negative.

Case 12. (Effect of chilling in a moderately allergic child.)

M. D., aged three years and nine months, had many asthmatic attacks from the age of three months which were usually associated with infections. He responded well to food elimination and antibiotics. However, when careful attention was paid to the prevention of chilling this boy had only two attacks of asthma in over 18 months in spite of an unrestricted diet. Both asthmatic episodes were associated with chilling. The father, a pediatrician, observed him closely.

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Discussion (Abstract)

Dr. Sidney F. Pakula, Kansas City, Mo. The recurrent upper respiratory infection is the most frequent of all pediatric illnesses and is the bane of the pediatrician's existence. Few of us have escaped the experience of the mother who returns at regular intervals with the complaint, "My child has another cold." The cold and upper respiratory infection may be synonymous.

Dr. Halpern has told you of the necessity of a very careful appraisal of the underlying etiologic factors in recurrent upper respiratory infection, and that control of these factors can be achieved by the cautious application of these procedures: allergic management, the elimination of possible environmental factors, and the judicious use of vaccines and antimicrobial agents.

I would like to emphasize again what he has said, that the inadequately evaluated child will be an incompletely treated one. Limited methods formerly employed, because we did not thoroughly investigate underlying principles of etiology, can no longer be condoned. For example, the increased recognition of underlying allergic disease in many children with lymphoid hyperplasia, has led to a re-evaluation of the need for surgical treatment with respect to the tonsils and adenoids. Unless there is good evidence of local disease producing complications, the surgical condition is strongly contraindicated.

Where the procedure is employed, it should be performed only after the fundamental allergic process has been completely investigated, treatment instituted, and the patient maintained in a good state of allergic control after surgery. Not infrequently, the surgical removal of the adenoids is followed by hyperplasia of the lymphoid tissue which is an integral part of the mucous membrane of the nose and throat, resulting in the formation of nodules in the nasopharynx. These areas have long been known to be the starting point for infection in the upper air passage, giving rise to repeated attacks of sinusitis, otitis media, and upper respiratory disease. In selected cases, irradiation with x-ray, properly shielded, in doses small enough to cause no harm to the skin, or interfere with growth centers, is indicated when administered by a qualified radiologist.

Aggammaglobulinemia is a relatively new disease entity. The term was first introduced by Col. Ogden C. Bruton of Walter Reed Hospital, to indicate a deficiency in gamma globulin, either congenital or acquired which permits of multiple recurrent infections, especially of the upper respiratory tract, and

the skin. A small percentage of children are extremely susceptible to reinfection by pyogenic cocci, the influenza bacillus, and the members of the gram-positive group. They do not respond to artificial immunization, (especially against diphtheria), maintaining a persistently positive Schick test, and vary markedly in their leukocyte count, (either very high or very low), clinically. They have a succession of bacterial infections, usually beginning in midinfancy, characterized by pyodermia, sepsis, and infection of the upper respiratory tract. However, they handle the common viral infections very well.

The mechanism of production of this disease condition is a primary one in which the patients just cannot make gamma globulin, or when they do produce gamma globulin, either lose it through the urine, or rapidly metabolize and destroy it. One assumes that the antibody formation process resides in the gamma globulin fraction of the blood, and that ordinarily the individual's resistance to gram-positive organisms is dependent upon antibody formation. Since this element is absent in these patients, of necessity there must be an addition of gamma globulin fraction, (as found in commercial pooled gamma globulin), to the usual therapy of antibiotics, and chemotherapeutic agents, usually employed in treatment.

It is not too difficult for the average physician to determine by relatively simple screening methods which of his patients are so affected. Since we know that patients with a gamma globulinemia do not respond to attempts at artificial immunization, especially against diphtheria, the finding of a persistently positive Schick test in such individuals is presumptive evidence of a gamma globulinemia. Also, these patients with blood types of either 0, A or B, will show a lack of isohemagglutinins which are normally present, in the gamma globulin fraction of the plasma.

The treatment is relatively simple and sometimes dramatic. It is the addition of pooled gamma globulin, where indicated, to the already instituted, accepted treatment in those cases showing a failure of response, or poor response to adequate antibiotic therapy. For example, many children acutely ill with laryngotracheobronchitis, receiving antibiotics, oxygen, humidification with alevaire, etc., show an almost immediate pick up in their response, shortly after the administration of a sufficient dose of gamma globulin. Since the introduction of gamma globulin therapy, we have had no fatalities in a fairly large series of severe laryngotracheobronchitis, and the need for tracheotomies has been reduced significantly. The dosage employed is not too well stabilized, depending upon the history of recurrence of infection, and the severity of the disease at the time the fraction is administered, varying from a single dose of 1.0 cc., to one of 0.3 cc. per pound of body weight. In our experience we have not found it necessary to administer the very large doses advocated, since we are convinced that many of the responses are purely qualitative, not quantitative.

In the prevention of recurrent respiratory infection, gamma globulin combined with a mixed respiratory stock vaccine has been helpful. It is noteworthy that the size of the dose of mixed vaccine can be reduced considerably when given in combination with gamma globulin, and the intervals between injections increased to four week periods, or more. Our standard procedure is to give 0.25 cc. mixed respiratory vaccine and 0.5 cc. gamma globulin, increasing the dose once weekly for three weeks, and then at four week intervals, beginning before the usual time of onset of the respiratory season in our community and ending about the time of the spring or Easter holidays, for school children. Such a program has proven helpful in lessening the incidence of recurrence of severe upper respiratory infection; for children in whom no allergic process is demonstrable, or in those in whom the underlying allergic factor has been controlled by adequate therapy, the combination of small doses of vaccine and gamma globulin, perhaps with the addition of antibiotics as employed in the prophylaxis of rheumatic fever might constitute a usable guide in prophylaxis of recurrent upper respiratory infections.

Dr. Carroll M. Pounders, Oklahoma City, Okla. I think this is an excellent paper and I am in accord in a general way with the efforts to protect children from infections. However, I want to warn against the possible penalties of too much protection against minor infections. Our higher incidence of poliomyelitis, for example, could be a penalty for good protection and sanitation. If the program against these minor illnesses is carried out too conscientiously one might instill an attitude of too much fear and overprotectiveness in parents. After all, the only reason any of us survive is because we develop immunity to the common infectious diseases and manage to get along with our environment. So, I would be hesitant to take all these children out of play school. I do not wish to appear too callous about this matter, but I feel that they must develop their own immunity to many of these infections. If more severe conditions come into play, we now have excellent methods of controlling most of them and do not have to worry much about such things as pneumonia or even otitis media.

Dr. Homer Prince, Houston, Tex. I want to congratulate the essayist on the very practical paper he has presented. I think it is going to mean much to all of us.

I would like to emphasize one or two things he pointed out. These children in the beginning are quite frequently infected and at that stage their infections are more violent, with higher fever, but as they go along they get more frequent infections with lower febrile response, all the time developing a higher grade of allergy, often to the infecting organisms. Protecting the children in the early phases saves much trouble later. If their allergy balance can be maintained normally by controlling their infections, I believe they will not develop increased sensitization at a later date.

I would like to point out that we are seeing more frequently one organism as an infecting agent as a result of widespread use of many antibiotics; I refer to *Pseudomonas aeruginosa*. This is a very allergenic organism but, on the other hand, the sensitization to it ordinarily will respond very well to vaccine therapy. Pseudomonas infections frequently require polymyxin or bacitracin for their control. We have adopted the practice in children in whom we have demonstrated

this organism of having the parents procure aerosol equipment to give these antibiotics at home, once or twice a day, for long periods of time and I believe with good results.

Dr. Halpern (Closing). I should like to thank the discussants for their comments.

Dr. Pakula has brought to the fore some of the more pertinent factors about the use of gamma globulin in the treatment of infections. I was not familiar with this new x-ray technic for demonstrating lymphoid tissue. If this should prove successful, it would be an excellent guide in the management of these children who might require gamma globulin.

Dr. Pounders, I would not advise taking those children who had minor illnesses from nursery school. Perhaps I was not definite enough, or emphatic enough in explaining that I referred only to those children who developed the severe forms of otitis media, bronchitis, cervical adenitis or sinusitis and that required eight to ten days, or longer, of antibiotic therapy. I think, too, that the child with minor colds should be observed; and I feel as you do about the natural evolution of this disease. However, there are children who may not be able to attend nursery school at age three who can at ages four or five, and since there are three preschool years, it still gives that child ample time to acquire immunity before entering first grade.

The whole subject of antimicrobial therapy and gamma globulin and its relation to the development of antibody protection is at this time, I believe, in a more or less philosophical stage. I think there are too many arguments pro and con, that it is difficult to enter into any such discussion because we lack sufficient factual information.

I certainly appreciate the comments of Dr. Prince. I feel, too, that many of these infections after having passed through the severely acute phase become indolent. They hang on and on and often times these children have a low grade fever, temperature of 99.5 to 100.5° with a normal white count. These findings are enough to account for the additional overloading that breaks down the allergic balance. But the point that I tried to bring out was there are many ways to attack the problem of recurring acute respiratory infections. In some children it will be easier to use one method and in others a different one. There are many means available to us and the painstaking time spent with the patient will demonstrate which is the best procedure for a particular child. In many instances any one of the methods described in the body of the paper will produce good results.

Celsus on Epilepsy

That malady which is called comitialis, or the greater, is one of the best known. The man suddenly falls down and foam issues out of his mouth; after an interval he returns to himself, and actually gets up by himself. This kind affects men oftener than women. And usually it persists even until the day of death without danger to life; nevertheless occasionally, whilst still recent, it is fatal to the man. And often if remedies have been ineffectual, in boys the commencement of puberty, in girls of menstruation, has removed it. Now sometimes there is a spasm of the sinews when the man falls down, sometimes there is none. Some try to arouse the patients as is done in the case of those affected by lethargy; which is quite useless, both because not even the lethargic patient is cured by this method, and because, though it may be impossible to awaken him and he may thus die of starvation, the epileptic, on the other hand, returns to himself. If a man falls in a fit without the addition of spasms, certainly he should not be bled; if there are spasms, at any rate he should not be bled unless there are other indications for the bleeding. . . .

—From De Medicina book III 23. Translation by W. G. Spencer, London, Heinemann.

Anorectal Abscesses and Fistulas*

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The author outlines his thoughts on the etiology and management of anorectal abscess and fistula.

ANORECTAL ABSCESSES AND FISTULAS have provided a topic for discussion as far back as recorded medical history can be traced. Numerous theories and treatments have resulted. Earlier conclusions were biased by timidity, ignorance and the lack of therapeutic and scientific adjuncts which we consider commonplace now. Many conclusions have been modified from those that seemed rational by the previous experiences of those attempting anorectal surgery. The extensive use of the cautery by some surgeons illustrates the latter type of conclusion. Fear of incising the external sphincter muscle often results from ignorance of the anatomy of the region, combined with a lack of knowledge of the nature of a fistula, the inability to follow dexterously the tract or tracts, or to employ the judgment which comes from sound instruction by those familiar with these lesions.

Etiology of Abscess

Anorectal abscesses may be simple or complex. Fundamentally they all appear to arise at the level of the dentate margin. The embryologic development, the physiologic function, the variability of the fecal material evacuated, and the lymphatic drainage of the tissues in the region of the dentate margin all may be factors in the origin of the abscesses and subsequently the fistulas.

More recently there has been considerable discussion concerning the part the anal glands play in the etiology of abscess and fistula. That they may play a part seems undeniable, but until it can be demonstrated that these glands are distributed anatomically in those situations in which fistulas and abscesses are prone to originate I am inclined to withhold judgment. The fact that nearly 90 per cent of the primary sites of infection producing abscess and fistula are in the posterior midline (56 per cent) and the anterior midline (31 per cent) and the remaining 12 per cent are situated laterally requires study to prove that anal glands are similarly distributed. If this is not proven, the traumatic factors, the mere anatomic weakness, and crypts must suffice to explain the primary sites.

In explaining the formation of an anorectal abscess the stages described by Dr. Buie seem sufficient and logical, briefly: (1) the injury or infection of a crypt; (2) the extension of the infection; and (3) the formation of the abscess.

The site of the development of an abscess varies greatly, and the efforts to account for the various sites has led to diverse theories. Doubtless there is some basis for these theories but they have always seemed relatively unimportant with regard to the correct diagnosis and treatment of anorectal abscesses.

Anorectal abscesses have acquired names related to their anatomic location, e.g., subcutaneous, submucous, ischiorectal, perianal, perirectal, right or left pelvirectal, supralevator, infralevator, horse-shoe, sprinkling pot, etc. Additionally, a single anorectal abscess may be present in several locations which would increase the nomenclature. In my association with students of proctology, it seemed to me that their understanding of anorectal abscesses was clarified if, at first, all attempts to employ the names referring to anatomic location were avoided and the basic understanding of the formation of the abscess and its possible variation was established. At times it appears that we would bury the very facts we are trying to emphasize in a deluge of nomenclature.

Diagnosis of Abscess

The prompt diagnosis of an anorectal abscess may be important to the patient's health. An accurate history of the patient's discomfort, its duration and possible variability, to-

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gether with any information relative to physical or physiologic functions which intensify the pain, assist materially. This typical history may be varied, however, by the occurrence of a sudden rapid increase in the intensity of discomfort. On incising abscesses in patients who have presented this latter symptom I have found that the abscess contained some clotted blood in addition to pus. This has lead me to conclude that the inflammatory process eroded or otherwise caused the rupture of a blood vessel in the wall of the abscess, thus initiating a comparatively rapid increase in the pressure within the abscess, resulting in the rapid increase in the intensity of the patient's discomfort.

Occasionally abscesses above the level of the dentate margin will produce a defecatory urge. Large abscesses situated laterally to the rectum may cause pain in the lower extremity on the involved side.

Abscesses situated on either side of the anus can be detected by the resulting alteration of the contour of the involved side confirmed by digital examination.

The examination is of utmost importance but this should always be accomplished with care and gentleness. Palpation, digitally, is probably the most important diagnostic method. In practice, it is well, if there is a clue to the involved side, to palpate the normal portion of the perianal, anal or rectal tissues first, then gently to feel the involved area. Usually it is not necessary to press firmly. Often this is undesirable because, in addition to causing unnecessary pain, compression of tissue may hide the abnormality being sought. In anal abscesses bidigital palpation may be necessary and without such palpation a small abscess buried in the anal tissues may be overlooked. A smooth or irregular elevated area characterized by fluctuation, with a surrounding zone of firmness is often sufficient to assure the proper diagnosis. Localized tenderness may be very acute but in some instances, especially when the abscess is above the dentate margin, tenderness may be lacking.

Some abscesses occur and recur without rupture or incision, because when the pressure within the abscess cavity becomes sufficient it will cause spontaneous drainage through the site of the primary infection or crypt. These abscesses usually present a firm, nonfluctuating mass on palpation, and if the point of origin is observed and pressure exerted on the surface of the abscess pus may be seen escaping through the site of the infection's origin.

Treatment of Abscess

The treatment of an abscess can be described briefly as "incision and drainage." There are two schools of thought regarding the time to incise the abscess. One insists that the abscess should be incised immediately after the diagnosis is made. The other suggests the application of heat until the abscess presents superficially. I have always leaned toward the latter school for several reasons: (1) abscesses external to the anus usually drain more satisfactorily when the drainage is unimpeded by subcutaneous fat; (2) frequently when the abscess has become superficial it is easier to determine the site of infection and that will prove advantageous when the subsequent operation for fistula is considered; (3) the added time permits more satisfactory "walling off" of the abscess and makes the fistula operation simpler.

Incising an abscess external to the anus requires some judgment and should not be attempted by routine incision. If the tract leading toward the site of the original infection can be detected by palpation, the incision should be as close to this as possible. Ordinarily the incision should be made parallel to the nearest anal margin. I have found it simple to make a single incision and then pick up each side of the incision and remove these with a pair of curved scissors producing a satisfactory result with a procedure which is easy mechanically. Following the incision I have never felt it necessary or helpful to pack the abscess cavity. Local application of heat seems beneficial. Digital exploration of the cavity should be avoided unless it is particularly indicated and then only with utmost gentleness.

Prior to the advent of intravenous anesthesia local infiltration anesthesia seemed the most desirable, but its use often causes as much pain as a direct incision if the abscess is superficial and fluctuant. Intravenous anesthesia now seems so desirable that I am inclined to employ it as much as possible for incision of an anal abscess.

Abscesses above the level of the dentate margin also require drainage; usually this can be accomplished by means of a small incision through the mucous membrane followed by the insertion of a curved forceps into the abscess cavity. After the insertion of the forceps the blades should be opened slightly and the forceps be withdrawn. The incision should be as low as is reasonably possible in order to facilitate the subsequent operation for a complete internal fistula.

Following incision and drainage it is advantageous to permit the acute process to subside before attempting fistulectomy. This may seem a waste of time to the patient, but it can be explained readily that during the interval between the procedures the abscess cavity will become much smaller and the fistulectomy therefore much less extensive. This waiting period also permits the scarring resulting from the abscess to become organized which will help to prevent retraction of the sphincter muscle if it is necessary to cut through it. May I also add that it has always seemed expedient and logical to tell the patient before incision of an abscess that a fistula will doubtlessly result, and to explain why this occurs, since a patient left to his own conclusions may feel that the surgeon is responsible for the fistula because of an improper procedure.

All patients having an anorectal abscess should have a sigmoidoscopy, if not prior to incision and drainage, then surely during convalescence when the acute tenderness has subsided. During the patient's convalescence the etiologic factors, other than the typical anorectal abscess, must be considered. In the presence of an abscess the differential diagnosis may be considered, but regardless of the etiology the abscess should be incised to provide drainage and the etiology seems to be relatively unimportant at the moment. After incision and drainage this is not true and a conscientious surgeon will, without exception, consider all of the possible etiologic factors prior to fistulectomy. The exception to this rule would be the presence of a simple or multilocular retrorectal cyst. Usually the lack of pain or tenderness and the absence of any induration should arouse the surgeon's suspicion thus preventing the treatment advised for abscesses.

Etiology of Fistula

For brevity I will group together the fistulas resulting from anorectal abscesses and the sinuses in the perianal and adjacent gluteal surfaces appearing after spontaneous rupture or incision by another surgeon. The reason for this is to facilitate the discussion of the etiologic factors. To have a reasonable point at which to begin it seems sound to say that all such points of drainage indicate the presence of a fistula unless there is evidence to the contrary. Obviously, this statement is founded wholly on a percentage basis and does not provide an excuse for proceeding blindly without considering other possible etiologic factors.

I have included some rare causes of sinuses in the perianal and adjacent surfaces. Lacking statistical study I am compelled to list the following in a rather "hit and miss" order which I hope will be understood.

A *sebaceous cyst* may cause an abscess and, if the amount of inspissated sebum is sufficiently large, may produce a chronic draining sinus.

Tuberculosis per se is a rare cause for an abscess without a primary opening at the dentate margin. I have seen such an abscess and sinus in a young woman who had miliary tuberculosis accompanied by tuberculous peritonitis, a tuberculous kidney, and terminally tuberculous meningitis.

Bartholin cyst abscess may be mistaken for an anorectal abscess but in practice the error is usually reversed.

Abscesses frequently develop as a complication of *anal fissures* but there is usually little difficulty in arriving at the proper diagnosis.

Hidradenitis suppurativa, notoriously may produce a subcutaneous abscess resulting in a chronic draining sinus, but fortunately the progress of the disease and marked acne elsewhere should arouse suspicion and lead to the correct diagnosis.

Actinomycosis is a rare but not unheard of infection which may produce chronic draining sinuses in the perianal region. Strangely the patient may fail to disclose a history of an original abscess because the external lesion may resemble only a small furuncle with persistent drainage. Firm, board-like induration, with more than one sinus usually, or ano-

rectal fistula and possible rectal involvement helps to make the diagnosis which ultimately depends on microscopic study and discovery of the causative actinomyces.

Osteomyelitis of the bony pelvis may also produce abscesses and chronic draining sinuses which may closely resemble a fistula.

Urethroperineal fistula may resemble a fistula anteriorly to the anus, but usually a careful history will disclose the difference. Rarely is it necessary to examine the patient under anesthesia to verify the diagnosis.

A *carcinoma* or epithelioma at, or just above the dentate margin may be the site of origin of a perianal abscess and subsequent fistula. I have seen several in which the recent history of an abscess reasonably seemed to post-date the malignant lesion. In each instance the tissue destruction or loss had been sufficient so that a concavity resulted with an overhanging edge on the distal margin of the causative lesion.

Accidental wounds in the perineum and perianal regions heal rapidly if they are seen promptly, investigated thoroughly and cared for properly. Occasionally, a patient having had such an accident and cared for by some other physician may present himself because of a persistent draining sinus. The first problem then is to determine by exploration and roentgenologic studies whether a foreign body is present or not. Removal of such an object usually results in prompt healing. I have seen only one instance where a sinus persisted in spite of the fact that no foreign body was present and bacteriologic studies failed to disclose any unusual infection.

Dr. John R. Hill observed a patient in whom a perianal sinus was present which was proved roentgenologically to originate in a *sigmoid diverticulum*.

I realize that some of the cases mentioned are rare but I have included them for the purpose of emphasizing the need for alert conscientious consideration of all perianal sinuses prior to surgical intervention.

Treatment

Having eliminated all other possibilities and assuming that we are considering an anorectal fistula there can be no doubt that, at the present time, surgery offers the only cure. Such surgery should be accomplished intelligently, expeditiously, with a minimum of trauma and loss of tissue. There are a variety of ways of doing a fistulectomy but within the limits stated the method means little if the result is satisfactory.

It seems impracticable to attempt to diagnose tuberculous fistulas preoperatively or to modify materially the surgical method of doing a fistulectomy in such cases. Salman's rule has proved to be correct in many instances but incorrect so frequently that it seems to be of only limited practical value.

Each fistula must be cared for individually. Under satisfactory anesthesia, which provides muscle relaxation, it is best to inspect, palpate, probe and determine the primary opening. One should start operating from the primary opening when possible, or from the secondary if it is more expedient mechanically, or from both directions if necessary. Incision should be done only when the tract is recognized, all of the tracts must be uncovered and only that tissue which interferes with drainage or would prevent the best possible result "cosmetically" should be excised. It has been my practice to use as few instruments as possible because unnecessary clamps and retraction often produce as much interference as help, and can be the cause of unnecessary trauma if handled carelessly by enthusiastic but inexperienced assistants.

In accomplishing a fistulectomy the essential procedure consists of exteriorizing all tracts if the fistula is external, and to uncover all tracts above the level of the dentate margin if dealing with an internal fistula. If the fistula is a combined internal and external one, the surgical procedure must also consist of a combination of both procedures.

I have been impressed by the amount of information concerning a fistula that can be learned by palpation after anesthesia has relaxed the perianal and levator muscles. By palpating carefully and without exerting too much force it is often possible to learn more than by direct probing. It is surprisingly easy to insert a probe through the wall of a tract into subcutaneous fat or any of the potential tissue spaces. If the tracts are palpated prior to probing the error mentioned can be easily detected.

I find that fistulas originating in the posterior midline and extending around the anus

to present the secondary opening laterally often prove very difficult to manage because of the frequency with which a sharp proximally directed angulation, or small abscess will prevent the ready disclosure of the fistulous tract. Contrariwise many of the fistulas with several or more secondary openings have responded to simple surgical procedures even though disquietingly extensive. Because of the ease with which a side tract may be overlooked, it has seemed expedient to continue search for such tracts diligently from the moment a tract is disclosed until all trimming of the wound margins and suturing has been accomplished.

Some fistulectomies require no suturing, but if the incision into the primary opening permits the mucosa to retract it is advisable to employ sutures to replace the retracted edge at the level of the normal dentate margin. Occasionally, when the tracts are deeply seated it is practicable to place a continuous locked suture or interrupted sutures through the edge of the tract and, skipping the subcutaneous adipose tissue, to insert the needle subcutaneously to approximate the skin edge toward the tract margin. The purpose being to avoid a loose, tender, "flapping" skin edge and to permit more comfortable dressings.

Some have advocated an incomplete fistulectomy employing a seton through the medial portion of the fistula until the lateral portion is nearly healed after which the tissue overlying the seton is incised. The only time the use of a seton has seemed advantageous to me has been in infants where surgery and postoperative care are impractical. Employing a seton and gradually tightening it will often produce a satisfactory result.

Only in rare instances is it necessary to use a two-stage operation. In those cases in which two or more fistulas are present I cannot find any basically sound reason for not operating on all fistulas at the same time. In the presence of chronic ulcerative colitis a fistulectomy should be avoided unless there are unusually urgent reasons for doing it.

It is possible that the correct name of the operation recommended is fistulotomy instead of fistulectomy, because I have never been convinced that it is necessary to remove the fistulous tract except in rare instances, when approximating the margins of the distal portion of a long wound to obtain primary healing seemed practicable. The original basis for removing the fistulous tract was apparently predicated on the notion that the tract was an infected membrane, but one asks when is any anorectal wound sterile? The margins of the tract extending through or proximal to the sphincter muscle serve to assist in avoiding retraction of the incised ends of the muscle insuring as much control as possible. If the tract is lined with exuberant granulation tissue this is removed with a curette or a gauze sponge.

Only rarely would it seem advisable to avoid operation, as for example in a case I saw six years ago in which a very complex fistula with widespread external openings also presented a retrorectal abscess that perforated through one of the sacral foramina. It seemed that any conceivable operation would produce more destruction and harm than the palliative expedient of curing the external secondary tracts and leaving the remaining tracts.

Postoperative care need only consist of keeping the wounds mechanically clean with warm irrigations after evacuations, the application of a mildly antiseptic solution, ointment or powder, and a satisfactory dressing changed as frequently as necessary. Packing fistulectomy wounds causes unnecessary pain at the time of the insertion and the removal of the packing, but, more important, doubtlessly is often responsible for incontinence. In wounds which seem slow in healing a change of the medication applied to the wound surfaces appears helpful. It is advisable to pass a small cotton tipped applicator through the depths of the wound to prevent "bridging." In tuberculous fistulas judicious exposure to ultraviolet light locally and to the patient's body in general assists healing after fistulectomy. In young individuals wounds which show little or no tendency to heal, regional ileitis or colitis must be suspected even though no symptoms have become manifest.

The patient is often concerned about anal continence. It is sound judgment to discuss this frankly with the patient, explaining at times so much tissue destruction occurs preoperatively that no surgical procedure will insure control but that everything surgically possible will be done to preserve control. Basically it is best to be frank rather than evasive and be hounded later by regret. No

surgeon can perform miracles or replace, to the satisfaction of the patient, tissue destroyed by an inflammatory process.

Conclusions

In conclusion, may I say that I realize I have not been able to include many factors and variations which may seem important to some. The time allotted did not permit. I have tried to present practical advice and conclusions based on my personal experiences. My purpose is not to disagree or argue with others, but merely to suggest that which appeals to me as being basically sound at the present time and that which has produced the most satisfactory results. I sincerely hope that as newer theories and methods are expounded we will be able to weigh them soundly and adjust our present concepts and methods accordingly.

Discussion (Abstract)

Dr. Raymond L. Murdoch, Oklahoma City, Okla. About 95 per cent of anal fistulas are due to infection in anal crypts with transmission to a perianal location often involving anal ducts and glands with abscess formation and discharge externally, internally near the crypt, or both. The internal opening is much oftener near a posterior anal crypt. The resulting infected tract may discharge externally posteriorly, but often dissects far laterally or elsewhere. Fistulas arising from crypts in the anterior half tend to have their infected tracts in a radial direction discharging on the perineum. The Bartholin gland may be secondarily involved in the inflammation. I have seen numbers of cases of persistent discharge after fistula operations, which did not clear up until more complete removal of infected Bartholin gland was done. This happened oftener on the left side.

We start all fistula operations with a slightly curved hook rather than a probe. A small-beaded eye tenotomy hook works very well. For years we have not injected dyes nor opaque material. Reasonable pressure is made on the instrument and the fistula opened that far. The granular floor is wiped. A remaining tuft of granulation tissue may indicate the continuation of the tract at a different angle. The probe-hook may be inserted into this and meet one passed into the internal opening. A fistulotomy with adequate "trim-back" of the edges and curettage of the base, is done oftener than a fistulectomy. Adequate drainage is the foundation of successful fistula surgery. This requires cutting the sphincter overlying the fistula. In a few cases after distal incision a seton is placed in the higher part of the tract and that encircled sphincter is severed under local anesthesia at a later date. Nearly always all sphincter overlying the fistula is severed at one operation. Sometimes the anal contour is helped by suturing some loose ends of sphincter with fascia down into the bed of the defect, not necessarily to corresponding sphincter across it. All gauze packing is usually gotten out within 30 hours. The sphincter ends are not thereby packed too much apart.

Sphincteric incontinence may be a complaint after some fistulas and the necessary incision of the sphincter over them. The operation for the restoration of control usually requires the adequate mobilization of the anorectal wall and the restoration of the posterior anorectal angle, approximating with interrupted sutures the lateral anococcygeal muscular structures behind the anal opening which is diminished in size.

Dr. Charles C. Massey, Charlotte, N. C. Because of Dr. Smith's extensive experience in this field, I wish to ask him a question that has been asked many times and will continue to be asked when fistulae are discussed, namely: On failure to find the primary or internal opening, do you await further developments, or do you complete this operation, assuming the primary opening to be located at a definite place?

Dr. Patrick H. Hanley, New Orleans, La. I would like to emphasize one thought in the differential diagnosis of these obscure perianal sinuses, and that is in regard to the infected presacral inclusion cysts that rupture into the perianal area. Frequently, because of improper diagnosis, these patients have multiple operations for fistula-in-ano, which result in incontinence.

Dr. Smith (Closing). I wish to express my gratitude to the gentlemen who have discussed my paper.

I do not treat acute abscesses as radically as Dr. Murdoch does. It has always appeared logical and advantageous to permit sufficient time to elapse to permit the acute inflammatory process to have ample time to "wall off." During the time mentioned the abscess cavity becomes smaller thus requiring less extensive surgery. Additionally, during this time sufficient fibrosis will form so that if it is necessary to incise the sphincter the resulting muscle ends will not retract.

Before the days of sulfa compounds and the antibiotics I treated an acute abscess radically with a totally unjustifiable result. My attitude since then, biased by that experience, has been to avoid handling acutely infected tissue whenever possible.

Concerning the question, "When you fail to find a primary opening do you go ahead or wait?" I find it difficult to answer this question briefly. Ordinarily it would seem logical to search, first in the posterior midline, then in the anterior midline, and finally in the lateral portions of the dentate margin. In most cases the tract can be palpated to the site of the involved crypt and in such instances I have found it expedient to continue the incision through the indicated crypt. The results following this procedure have been satisfactory. Waiting, doubtlessly, would permit the formation of another acute abscess but would not provide assurance that the involved crypt could be discovered any more readily than it could at first. It is my impression that after the acute inflammatory reaction of an acute abscess has subsided, the direction of the fistulous tract and its possible point of origin can be determined more readily than during the presence of the acute abscess.

The Doctor's Role in Health Insurance*

JOE M. BOSWORTH, M.D.,† *Atlanta, Ga.*

The author points up the doctor's responsibility in not adding to the ever increasing costs of prepayment hospitalization insurance. Unnecessary hospitalization, drugs and study procedures raise the premium costs.

THE AMERICAN MEDICAL PROFESSION has consistently stood for relief of hospital and medical costs through the means of voluntary health insurance. So far the public has accepted this approach. The continued rising cost of health insurance is once again creating a tool for the supporters of government furnished medical care through taxation. We must not be lulled into the belief that government controlled medical care is definitely defeated. It is only a "banked fire" ready to flame again with sufficient breeze. If this be true, we in the medical profession as well as the public must put forth serious effort toward making our chosen plan of voluntary health insurance work. If our plan fails government furnished medical care is at our doorstep. It is the purpose of this paper to give you as physicians some idea of what you can do to control the cost of health insurance.

Insurance is a business enterprise totally self-supporting. No business can survive while continuing to operate at a loss. No insurance company can continue to pay out a dollar in losses while taking in only 90 cents in premium. This means simply that the cost of insurance varies directly with its losses. We have only one avenue of approach in this problem and that is the reduction of losses by whatever means we can find which will still allow the protection desired and are otherwise honorable and ethical.

The first and also the biggest contribution which the doctor can make in the reduction of health and hospital costs is through preventive medicine in its broadest sense. Those illnesses which we can prevent by immunization, public health measures, removal from exposures or eradication of vectors must be further pursued and the public better educated to seek such preventive measures.

This, however, is not the biggest problem in prevention. A much greater contribution can be made by both the private practitioner and the industrial physician in getting early treatment to patients in the prodromal stages of disease and degeneration. The early and adequate treatment of peptic ulcer will probably prevent later hemorrhage or perforation with a marked reduction in total medical cost. Likewise early and adequate medical treatment of infections, diabetes, metabolic deficiencies, emotional problems, degenerative diseases and many surgical conditions will not only markedly reduce the medical costs of these conditions, but will also reduce the loss of earning capacity of the individual and the productive loss suffered by the industry in which the individual works and the society he serves. The problem of getting patients in the early prodromal stages of disease has been a long and difficult one. It is in this role that the industrial physician is making his greatest contribution. The detection of these early signs of disease and degeneration by the industrial physician, at routine examinations of masses of supposedly well individuals, allows him the opportunity to persuade these patients to seek early care for their problems. There is no greater servant or friend to the private physician, the public, industry and society as a whole than the industrial physician in this role. Many lives are being saved, disability prevented, and economic waste stopped by this industrial medical approach.

The second contribution which can be made by physicians toward reduction of health and hospital costs is the development of a more understanding attitude of medical economics. The unnecessary admission to hos-

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pitals and prolongation of hospitalization is costly. Although it may be more convenient for both physician and patient to observe routine cases of gastroenteritis, colds, tonsillitis, and the like in a hospital, it adds materially to the cost of hospital and health insurance and produces an increasing burden on the economic state of the public. The ordering of unnecessary laboratory, x-ray and physical therapy procedures is costly. The failure to stop administration of costly drugs when they are no longer necessary places an economic burden on our system of voluntary health insurance as well as the tolerance of the patient. The unnecessary prolongation of convalescence either by failure to advise return to work or by direct advice against work must be carefully guarded against. Many patients become hopeless neurotics because of too much time for self-pity. The unnecessary prolongation of convalescence also produces profound economic loss both to the individual and to society as a whole.

The third and newest contribution the physician can make toward the reduction of medical costs is through adequate rehabilitation of each patient requiring this for his return to work. This newer phase of medical care has restored many otherwise hopeless patients to a high degree of earning capacity and increased individual dignity. The combined efforts of physical medicine, surgery, psychiatry and vocational training have returned even a high percentage of paraplegics to useful work with marked reduction of their expected life-long medical costs. As more of these centers develop, the private physician must consider this phase of medicine as important as postoperative care. The greatest efforts in rehabilitation today are for those who have been injured, but there is no reason why this cannot be extended to include patients who have been disabled by disease and, finally, those who are victims of the aging process. Modern placement methods in industry, which measure the capacities of individuals as well as their incapacities, make many who have been considered totally disabled in the past now perfectly able to work within their own capacities.

The future of American medicine lies here. We must make our present system of voluntary health insurance work or accept the only alternative of government furnished medicine, paid for by taxation. This is a big decision. We can control it by our efforts but the efforts must be wholehearted and by all members of the medical profession, not by just a conscientious few. No, we cannot remain independent without being willing to pay the price. The price is learning to furnish good medical care at the lowest possible cost. This means an ever increasing effort to stop waste. It can be done and is being done by many today. It must be done by all.

Discussion (Abstract)

Dr. Hardy Kemp, Houston, Tex. I am Professor of Preventive Medicine at Baylor and in my department, with the help of a number of the men who look after the industries here, we teach an introduction to industrial medicine. We also include certain ones who are not physicians but who deal directly with the handling of claims, safety engineering, and industrial hygiene.

For the past seven years, it has been not only my good fortune, but my real pleasure to have acted on occasion as a consultant here in the Southwest for the company Dr. Bosworth represents. Thus I am familiar with some of the things he has mentioned. I can assure you that he could stand here all morning on this podium and tell you one story after another, every one of them true, and each one hitting just a little harder than the other. I do not know why he is pulling his punches; I think he wants us to come in and punch a little harder, which we will. It would be very well indeed if we all were to air our problems, ventilate a little as the saying goes nowadays, and draw from our own experiences those which would be helpful to us all. For example, I know of a plant hiring about 6,000 people located in a city in which the plant itself and its subsidiaries just about make up the city, as is often the case. In this instance, the group insurance benefits a worker could get, and in this instance most of the work-force is female, are so generous that by staying at home under a doctor's care, yet enjoying the mountain air and scenery while rocking in the rocking chair on the back porch, they could do about as well as they could working down at the factory. In fact, when they got a little tired of working that is precisely what they would do. The situation was getting very much out of hand when a new medical director came to the place. After he had gained the faith of his employees simply by his own integrity, and after he had gained the confidence and respect of the county medical society in the same way, he went to the county society and explained his problem to them. They said, "Well, doctor, in a way we have sensed all this, but we did not know it was quite as bad as you make it out to be." He said, "I am not exaggerating; as a matter of fact, I am minimizing if that could be possible." He said, "What can I do about it?" The reply as one man put it was, "Here is the problem. If I do not certify that Mrs. So-and-So is sick, then I feel that Mrs. So-and-So will not call me the next time a baby comes around, and I am not so sure—in fact I know they will not call me for other things they need

to have done. After all I have to live with this. Yet I do not want to surrender professional honesty in that way. I will just go as far as I can with you professionally, recognizing that medicine is an art as well as a science, and sometimes we are up against it. What is the answer? What can we do about it? Will we have some kind of a system of consultants or a panel of consultants?" That seemed impractical and cumbersome so that finally the upshot of the whole thing was, and this is my story, that this medical director with the help of the county society, actually the county society did it, was to develop a panel of single individuals who take in rotation controversial, or what could be controversial cases, and advise as to whether that person is well enough to go back to work. Fortunately, I suppose, the town is big enough to allow for enough anonymity, one might say, or impersonality to take care of things where there is a question of diagnosis. In any case it has worked out wonderfully well. It has not effected a complete cure you may well be sure, but it brought about a decided advantage, for as Dr. Bosworth points out to you, in instances of this kind we talk to three different people—three different elements: the practicing doctors, management officials, and labor. We should go to each of them. We should not be reluctant to invite ourselves to their conferences and to their meetings and to let them know our feelings and our problems. The men who make the wheels go around want to know, and they want us to tell them. If we can get the same kind of an invitation from labor, then we will cover all three elements. We can always talk with our own medical people, with or without invitation, but we may have to invite ourselves to meet management and labor. Yet we need to carry the message. Of that I am quite sure.

Dr. W. G. Thuss, Birmingham, Ala. I am fully aware of the problems that Dr. Bosworth has mentioned and we have talked many times about them. I would like to take one minute to make this suggestion to Dr. Bosworth to pass on to his insurance company.

It seems to me that some idea might be brought up by the insurance companies whereby the insurance such as mentioned by Dr. Bosworth can be put on a cost-plus basis.

Dr. Robert A. Wise, Houston, Tex. I will select only one out of the many subjects which Dr. Bosworth touched upon for discussion—namely, that at the present time in many companies with fine sickness benefits, the employee makes more money while he is sick than while working. To counteract this it is the responsibility of the company to keep the *esprit de corps* of its employees so high that they would prefer to work than to stay off. Excellent benefits for a company's employees are very good and usually go with high morale and good employee relations, but not necessarily so. To keep these benefits from being abused, it is necessary to keep this *esprit de corps* high.

Dr. J. W. Davis, Lynchburg, Va. I have been for the past two or three years co-chairman of Public Relations for the Medical Society of Virginia, and I believe that in improved public relations you are going to get a whole lot of these difficulties ironed out. If you will put on active and helpful public relations programs in between your state medical meetings, I think you will get helpful solutions to these problems.

Dr. John E. Echols, Richwood, W. Va. I would like to know what you think of a $50 deductible health insurance program, and whether it has been tried anywhere? We have a great deal of insurance abuse in West Virginia. Occasionally a person will come in with as many as six policies; they are making money out of this insurance. They have been disabled, and it is quite a problem. Furthermore, if you do not put them in the hospital, they will go down to Dr. Jim. He puts them in. So it is a very real problem.

Dr. Grady Rountree, Louisville, Ky. There is one plant that I know of, Dr. Bosworth, which has a total health insurance as far as hospitalization is concerned. If a person suspects that he may have an ulcer and he goes to this doctor and he says to the doctor, "Now, if you will send me to the hospital for the examination, why, it will be paid for, but if I have this examination in your office, the insurance will not pay for it."

I have talked to some of my friends about this type of thing, and they say it just puts us on a spot sometimes, because if they request sending them into the hospital for an examination, sometimes we almost have to do it. I wonder if you would enlighten us a little on that?

Dr. Edward Norfleet, Sapulpa, Okla. I also am part owner of a small 18-bed hospital and we do about 50 per cent industrial practice. Yesterday, I talked to Dr. Bosworth and I am sorry to say that no one ever thinks that the insurance companies are at fault. Some of these things are the fault of the insurance companies, too. For instance, one of the biggest industries in Tulsa near where I practice recently sold this hospitalization plan to their employees and they passed out a pamphlet, "Your Pass to Hospitalization." Well, they are indoctrinated in that, that this is your pass to hospitalization, and next week they come over here. A lot of the adjusters who come out are not aware of the problem.

I also would be very interested in knowing statistically how many of these isolated cases there are—I am sure Dr. Bosworth knows that you can get up at a medical meeting of this type and recall that they admit four people from one family. We have 40 beds and two hospitals in a town of about 15,000 people, and I would like to know how many of these towns are so overhospitalized that they can take four from one family. We cannot do it in my town, nor in many towns in Oklahoma that I know of. If that is so, it must be down in Georgia where the politicians have got Hill-Burton hospitals that they can put these patients in, but it certainly is not in Oklahoma. I would like to know statistically how many of these cases he knows of, how many of these cases these other doctors have described, because we certainly do not have it in Oklahoma. We do not have enough beds to put sick people in.

Dr. T. M. Tyndall, Beaumont, Tex. I would like to discuss what the doctor just stated about educating the people about it. I think we should educate the insurance companies, too, about the situation.

I cite this case about a lady who had a small lesion

that turned out to be a basal cell epithelioma on the dorsum of her hand. I called one of the insurance companies that she had her policy with, and she had two. They said, "No, Doctor, we won't pay for tissue report, we won't pay for surgery, we won't pay for anything except five bucks on emergency, if you run into emergency in your office, but if you put her in the hospital, we will pay the whole works." So I filled out two forms on this lady; her hospital operating room was $15, her private room was $10, her tissue report was $10, routine lab was $6, and I got $15 for it, filling out two forms which she had filled out in duplicate, and got her pay back on the second policy. Now, it behooves me that those things happen in insurance companies who will not allow you to do a small minor surgical procedure, dissection or incision, in your office, and save them, I would say at least on this case, $50 or $60. What do you think about that?

Dr. Bosworth (Closing). I think that is strictly up to management to decide what they want to do as to industrial examinations. My company and I do not believe any other insurance company would ever make an outright statement to management that you should or should not hire anyone. The only thing we can say is that if you hire a lot of people with chronic disabilities or evidences of impending disability, that obviously you are going to have to pay for it. It is strictly a matter for management to decide, as far as we are concerned. You can buy a Ford or you can buy a Cadillac. You can decide that you want to cut the lights off and save a little electricity, or you can leave them burning and pay the price. The same thing is true with management in the cost of their insurance.

In regard to Dr. Thuss' idea of a cost-plus basis, I would like to say this, and I think this is a common problem, that the doctors and the public have no earthly idea of how insurance premiums are made up. Ninety per cent of the health and accident insurance that is written today is a cost-plus proposition, particularly in the larger companies. To give you a simple example of how we will write today a health and accident insurance, we will take the incurred losses of the company last year and divide by .75 and that is the premium for next year, which is actually the expense of operating. When you get up to the bigger premiums, one million dollars and over, it is even less than that. Ninety per cent of health and accident insurance today is written on a cost-plus proposition. The difference between Blue Cross and most private carriers is that most private carriers give some consideration to the individual experience of one plant, whereas Blue Cross takes all of its losses, adds them up, puts the override on it, and then all premiums go up across the board. So if you are healthy, you are going to pay the price for somebody else who is unhealthy. That is the difference.

Esprit de corps was mentioned, and I think that is one of the most important things. I think industry has missed a bet in not reminding their employees of the fact that actually work is good for you. The proof of the pudding is in the fact that people who retire and do not have any useful purpose in life soon die, most of them within three to six years, as experience shows. It is a privilege to work, it is actually good medicine to work. Psychiatrists tell us that work actually is a necessity for our happiness, just like money is a necessity, and I think industry is missing a bet.

In regard to public relations between doctors and the public, I think it is one of the most needed things in medicine today. The public does not understand what we in the medical profession feel, and I think it is a tremendous challenge to us to do more of it. We have sat by and taken a lot of criticism as a profession, and very seldom have we come forward and put our side out in language which the public can understand. I think it is very much needed.

In regard to the deductible clause effect, that is a coming thing. The insurance industry is thinking this way. They want to meet the needs of the public. You probably heard that General Motors has sent out many thousands of questionnaires asking the public what they want in the way of automobiles and that is what they are trying to build. The insurance industry is trying to do the same thing in the field of insurance, it is trying to write what the public wants. You can buy insurance on anything if you are willing to pay the price. The problem is the price. I will insure any one of you in this building right now, standing on the top of a building threatening to fall, for $1,000, but the premium will be $1,200. Now that is the answer to it. You can insure anything that you want to insure. Lloyds of London will insure practically anything. They will insure against rain, or anything else, but you are going to pay the price. The whole purpose of this discussion is the price. It is not set by insurance companies. It is set by the public and its losses. To give you an example of the effect of it, in a certain state we have a place where the doctor's office is on one side of the hall and across the hall is legally the hospital. The doctors had the practice there of examining patients in the office and sending them across the hall to get their penicillin shots, and their losses were going skyhigh. We immediately suggested to the industry that they put in effect a deductible clause of $25 a case and their losses dropped 50 per cent in the first year. So that is the effect of the deductible clause and it is probably what we are going to have to come to more and more.

The idea of office versus hospital was brought up, as to why insurance companies do not pay for office procedures and force you to hospitalize certain patients which normally you could take care of in the office. The answer to that again is what the public wants. If you are going to pay for every office visit of a patient, you are going to run the cost of health insurance up tremendously. The same thing is true with collision insurance on your automobile. If you paid for every $5 scratch on your car, the cost to the insurance company would be about $7.50 minimum to pay for the $5 scratch. So the insurance companies cannot absorb that $2.50; it has to go back to you. So, in finality, actually, it costs you $7.50 to fix a $5 scratch if you pay it that way. The actual purpose of insurance is to protect you against large losses. I think the biggest problem that the public must understand is the basis of insurance, and the most common fallacy which is in the public's mind at the present time is that if I pay $100 this year for my health and accident insur-

ance and December 31 rolls around and I have not got my $100 back, then I am being cheated. Insurance is not a banking institution. The answer is that if that one individual had to go in for a herniorrhaphy or an appendectomy, it would take approximately three to four years' premiums to pay for that one hospitalization. The public does not understand that. I have talked to many, many people in industry who believe that if they put $100 in this year, they have got to get it back or they are cheated and a great insurance company is becoming exceedingly wealthy at their expense. It is not true. That is one of the greatest fallacies that we have in the public's mind today.

Finally we have education of the insurance companies which was mentioned. I believe most reputable companies in the business today welcome any suggestions which doctors have to offer to improve the system. It is your system we are trying to serve. It is your system and the public's system, and we welcome all suggestions that any doctors wish to make.

GOLDEN ANNIVERSARY CELEBRATION
SOUTHERN MEDICAL ASSOCIATION

The Read House, Chattanooga, Tennessee

October 2-3, 1956

It will be remembered that upon call of Dr. G. C. Savage, then president of the Tennessee State Medical Association, Nashville, in 1906, representatives from Alabama, Florida, Georgia, Louisiana, Mississippi and Tennessee met at The Read House in Chattanooga, October 2-3, 1906, and organized the Southern Medical Association. At later meetings other states were added, making the sixteen states and District of Columbia now comprising the Association. The Council of the Southern Medical Association at the annual meeting in Houston, Texas, November 14-17, 1955, unanimously approved a suggestion that the Association have a Golden Anniversary Celebration at The Read House in Chattanooga, October 2-3, 1956, exactly fifty years from the day the Association was organized. The Council designated Mr. C. P. Loranz to be chairman of the Celebration Committee, the President to appoint the other members of the Committees. Since the Association was organized in Chattanooga, it has held one of its annual meetings there, its sixteenth, November 1922.

Celebration Committee

Mr. C. P. Loranz, Advisor and Professional Relations Counselor, formerly Secretary-Manager, Southern Medical Association, Birmingham, Chairman

Dr. Guy M. Francis, President, 1956, Chattanooga and Hamilton County Medical Society, Chattanooga

Dr. Charles R. Thomas, Member of Council, Southern Medical Association, Chattanooga

Dr. R. H. Kampmeier, Editor, Southern Medical Journal, Nashville

Mr. V. O. Foster, Executive Secretary-Treasurer, Southern Medical Association, Birmingham

Mr. Robert F. Butts, Business Manager, Southern Medical Association, Birmingham

Honorary Advisory Celebration Committee

Dr. J. P. Culpepper, Jr., President-elect, Southern Medical Association, Hattiesburg, Chairman

Dr. J. Morris Reese, Chairman of Council, Southern Medical Association, Baltimore

Dr. Milford O. Rouse, Past-Chairman of Council, 1955, Southern Medical Association, Dallas

Dr. Olin S. Cofer, Past-Chairman of Council, 1954, Southern Medical Association, Atlanta

Dr. Edward T. Newell, Past Member of Council, 1926-1931, Southern Medical Association, Chattanooga

Dr. John B. Steele, General Chairman, Southern Medical Association meeting in Chattanooga in 1922, Chattanooga

Dr. Willard Steele, President of Chattanooga and Hamilton County Medical Society when Southern Medical Association met in Chattanooga in 1922, Chattanooga

Dr. S. S. Marchbanks, Secretary-Treasurer, Chattanooga and Hamilton County Medical Society when Southern Medical Association met in Chattanooga in 1922, Chattanooga

Dr. Cecil E. Newell, President, 1955, Chattanooga and Hamilton County Medical Society, Chattanooga

CASE REPORTS

Demerol Intoxication: Successful Treatment with Nalorphine Hydrochloride

MILTON ENDE, M.D., and E. P. YERBY, M.D.,† *Petersburg, Va.*

THE DRUG NALORPHINE (Nalline) has been found to be an unusual antagonist to the effects of morphine, Demerol, Dilaudid, and other respiratory depressants. This is a case of Demerol overdosage with recovery, the quantity reported being the largest given at one time intramuscularly. The case also points out the danger of permitting inexperienced personnel to give injections in the home.

A 64 year old colored woman had been treated for approximately four months because of hypertensive arteriosclerotic heart disease and congestive failure. The usual treatment of digitalis, ammonium chloride, antihypertensive drugs and frequent mercurial diuretics had been used. However, she continued to get worse requiring more and more diuretics, and it was felt that hospitalization was indicated. The patient, however, refused to go to the hospital because of financial reasons.

She had not been able to sleep for three nights because of severe dyspnea, and it was felt that some relief should be attempted in the home. Accordingly, a 30 cc. vial of Demerol was prescribed, with instructions that 2 cc. be given each night at bedtime. The patient said a nearby "nurse" would give her the injection. She was instructed to have the nurse call the physician before giving the medication. However, this was not done. At approximately ten o'clock at night the entire 30 cc. vial of Demerol was given at one time intramuscularly. At 10:45 p.m. the physician was called and told that the patient was in deep coma.

The patient was seen in the home a few minutes afterwards and at that time was found to be in profound shock, the pulse was irregular, she was sweating profusely and was in deep coma. Nalorphine, 15 mg., was given intravenously and the patient was sent to the hospital.

At the time of arrival at the hospital, she was still in severe shock with a blood pressure of 80/60, her usual pressure being in the vicinity of 170/110. The corneal reflex was absent; knee jerks could not be elicited. The chest revealed numerous moist rales in both lung fields; heart sounds were distant. An electrocardiogram demonstrated a bigeminal rhythm which had not been present earlier in the day. The chest film showed the heart to be greatly enlarged with extensive congestion and edema. The patient appeared to be in extremis.

Another 10 mg. of nalorphine was given intravenously and the respiration, which had been as slow as 8, slowly rose and by 2:30 a.m. had reached 18. On the following morning, at 6:00 a.m., the patient responded to questions. Her blood pressure rose over a period of 24 hours to 160/90. The bigeminal rhythm persisted and potassium chloride, 15 gr., was given orally three times daily for possible digitalis intoxication. On the third hospital day the arrhythmia had disappeared and the patient apparently had recovered without any ill effects. Curiously, her cardiac status and congestive failure also appeared to improve.

The only other treatment given during her hospital stay was oxygen, which was discontinued on the morning after admission.

Discussion

A review of the literature reveals very few reported cases of Demerol overdosage. Previous reports have dealt with the taking of large doses of Demerol orally. One was reported by Cohen[1] in which 1,250 mg. of Demerol were taken, with recovery; another by Rohmer[2] in which 1,500 mg. were taken by mouth in attempted suicide. This patient's depression was terminated by nikethamide. The largest recorded dose was described by Pinkerton and Rolfe[3] in which 2,000 mg. were taken orally.

Summary

A 64 year old colored woman with severe heart disease was given 30 cc. of Demerol at one injection. This is the largest intramuscular dosage recorded with recovery.

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UP TO THE PRESENT

Drugs Affecting the Autonomic Nervous System: Part I. Clinical Application in Gastrointestinal Disorders

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JULIAN M. RUFFIN, M.D.,† *Durham, N. C.*

A rapidly expanding group of drugs has been offered the medical profession as an aid in the management of disturbances of the secretory and motor functions of the gut. As a result it seems to the point to review the pharmacologic and clinical applications of these substances in light of the newer knowledge.

Introduction

THE RAPID INTRODUCTION OF DRUGS affecting the autonomic nervous system, along with conflicting claims and contradictory reports has left the practitioner, in many instances, confused regarding the real value of these agents in the treatment of disturbances of the gastrointestinal tract. It would seem appropriate therefore to review critically the present status of these drugs, both in relation to their pharmacology and their clinical application.

Inasmuch as the autonomic nervous system, in part, controls both motor and secretory activity of the gastrointestinal tract, it is logical that gastrointestinal disturbances, whether functional or organic, should be treated by the administration of drugs which influence one or the other of the two components of this system.

Although most of the actions of the autonomic nervous system are reflex in origin, it is well known that emotions can produce alterations in activity of various portions of the gastrointestinal tract.[1,2] William Beaumont, in 1833, recognized that changes in gastric function were associated with emotional reactions.[3] Wolf and Wolff,[4] in studies on fistulous subjects, demonstrated that hostility, resentment and anxiety were accompanied by increased vascularity, secretory, and motor activity of the stomach, while fear, apprehension and sadness were marked by depression of these functions. The colon likewise has been shown to respond to the emotions with either hyper- or hypo-function.[5] These emotional effects are mediated by means of the autonomic nervous system and may be at a conscious level. Tension from unconscious or repressed emotional states also plays an important role and may influence profoundly the activities of the gastrointestinal tract.[6] Although altered function is frequently seen in emotional disturbances, there is no evidence that this, *per se*, leads to organic disease.

The problem of altered function secondary to chronic emotional states may be approached in at least two ways. The first of these would be a direct attack on the emotional disturbances by psychotherapy, environmental changes, and other therapeutic agents. The second is an attempt to reduce either sympathetic or parasympathetic hyperactivity and thereby block the effects of the emotions. While the effects of the emotions upon the various functions of the gastrointestinal tract are important, of equal or even greater importance is the effect of disease upon these functions. Actually the introduction of the newer drugs affecting the autonomic nervous system has been designed primarily for the treatment of organic disease rather than emotional states.

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Neuro-anatomy and Physiology

A clear understanding of the anatomy and physiology of the autonomic nervous system is essential to the intelligent use of drugs affecting the gastrointestinal tract.

The sympathetic nervous system is comprised of the thoracolumbar outflow of the autonomic nervous system. It has its cell body of origin in lateral horn cells of T-1 to T-12 and L-1 and 2. The preganglionic fibers from these cells leave the cord with the spinal nerves of the same region. These fibers are medullated and form the white rami communicantes. The preganglionic fibers of the sympathetic nervous system run to ganglia where they either traverse the ganglion without synapsing or end in a synapse with the ganglionic cell body. The postganglionic fibers are not medullated and form the gray rami communicantes of the spinal nerves.

The parasympathetic nervous system has two portions, the craniotectal (vagus) and the bulbosacral. The cells of origin lie in the central nervous system at the level of the midbrain and medulla and in the second to fourth sacral segments of the spinal cord. Of the two, the vagus is the more important. Its fibers are distributed to the lungs, bronchi, heart, stomach, small intestine and the proximal portion of the colon. In contrast to the sympathetic nervous system, the ganglia of the parasympathetic system are located close to or imbedded in the structures innervated, the postganglionic fiber being relatively short. The parasympathetic innervation of the distal portion of the large intestine and the rectum is derived from the sacral outflow.

Since the gastrointestinal tract is dually innervated, both branches of the autonomic nervous system can alter function. The usual effects noted after stimulation of the parasympathetics are an increase in gastrointestinal motility and in secretion. In general, there is contraction of the muscular wall and relaxation of the sphincters. On the contrary, stimulation of the sympathetic nerves produces relaxation of the muscle wall and contraction of the sphincters. Recent studies suggest that this is not as clear-cut as heretofore believed since administration of potent anticholinergic agents has been shown to relax some of the sphincters as well as the muscle wall.

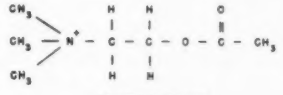
The autonomic nervous system can also be classified according to the type of chemical mediator used to transmit nerve impulses. The *cholinergically* mediated fibers which release acetylcholine from their endings are the autonomic preganglionic fibers and the parasympathetic postganglionic fibers. The sympathetic postganglionic fibers are *adrenergically* mediated.

The chemical structures of the chemical mediators are of importance in relation to drugs influencing the system. Acetylcholine is a quaternary ammonium compound and chemically it consists of an ester formed by the combination of choline and acetic acid.[7] Epinephrine and arterenol are closely related. The only chemical difference between them rests in the presence or absence of a methyl group on the nitrogen. The C-C-N linkage is common to all three compounds (Fig. 1).

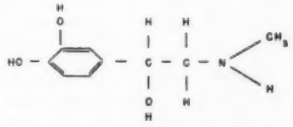
The newer drugs consist mainly of cholinergic blocking agents which do not interfere with the release of the chemical mediator but merely prevent the access of the mediator to the receptor. It would appear that this occurs because the blocking agent is similar in chemical structure to the mediator and has an affinity for the receptor.

FIG. 1

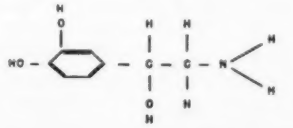
CHEMICAL STRUCTURES OF ACETYLCHOLINE, EPINEPHRINE AND ARTERENOL



ACETYLCHOLINE



EPINEPHRINE



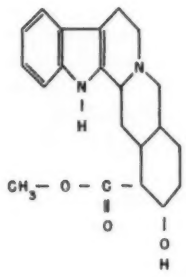
ARTERENOL

Pharmacology

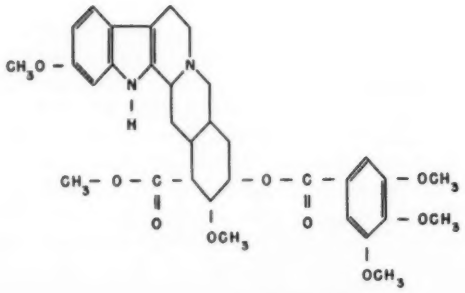
Adrenergic Agents. Substances which evoke physiologic responses similar to those produced by sympathetic adrenergic nerves are known as adrenergic agents. The two compounds found naturally in the adrenal medulla are epinephrine and levarterenol which is a levorotatory isomer. As pointed out previously, these agents are active only at the junction of the postganglionic fiber and the effector site. The effects of epinephrine on the gastrointestinal tract are complex. Usually there is inhibition of smooth muscle, but under certain conditions, stimulation may result.[8] Motor activity is inhibited by epinephrine using isolated intestine technic. In addition to the naturally occurring adrenergic agents, drugs such as ephedrine are available which have a similar effect upon the motility of the small intestine. There are a number of synthetic adrenergic agents, most of which have an alaphatic amine structure similar to that of ephedrine.

FIG. 2

CHEMICAL STRUCTURES OF YOHIMBINE AND RESERPINE



YOHIMBINE



RESERPINE

Of some interest in relation to the gastrointestinal tract are the adrenergic agents amphetamine and dextro-amphetamine, both of which have been employed to decrease appetite. Their mechanism of action is not clearly established, but is probably central.

Adrenergic Blocking Agents. Adrenergic blocking agents represent a recent advance in pharmacology. Yohimbine, although known since 1925, has been used little therapeutically. The recently introduced tranquilizing drug, reserpine, is closely related to yohimbine[9] and stimulates gastric secretion and gastrointestinal motility (Fig. 2). Other adrenergic blocking agents include piperoxan (Benodaine), Priscoline and dibenzaline. The one similar chemical feature of the newer synthetic agents is the presence of a tertiary amine which when converted to the quarternary or secondary form abolishes adrenergic blocking activity.[10]

Cholinergic Agents. The naturally occurring cholinergic drug is acetylcholine. Its principal effect is to produce an increase in tone and contraction of smooth muscle. Although its action upon the motility of the gastrointestinal tract is complex, its effect upon the secretory activity of the stomach is even more complex. It is generally believed that acetylcholine is a likely transmitter of responses from the vagus nerve to influence secretion, yet no increased output of HCl acid can be observed following its administration.[7]

The cholinergic drugs have been shown to cause an increase in the external secretion of the pancreas. This is particularly true of pancreatic enzymes, with less effect upon secretory volume and sodium bicarbonate.

Because of the evanescent action of acetylcholine, an effort was made to find a longer acting drug and acetyl beta-methylcholine or methacholine (Mecholyl) was synthesized. The actions of methacholine are generally those of acetylcholine in that it increases tone as well as contractility of the gut, and in large doses will cause nausea, vomiting and defecation. Unlike acetylcholine this compound causes copious production of gastric juice, rich in acid and pepsin. Although methacholine can be administered by mouth, it is

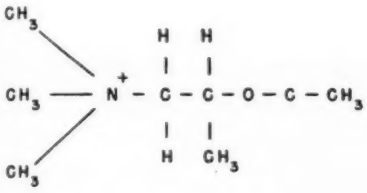
not well absorbed and is more effective given parenterally.

Carbamylcholine (Carbachol) resembles methacholine in stimulating both motility and secretion of gastric acid. However, the drug of greatest usefulness in this group is bethanechol (Urocholine) (Fig. 3). It is a carbamic acid ester of beta-methacholine and its action is similar to that of methacholine but more prolonged.

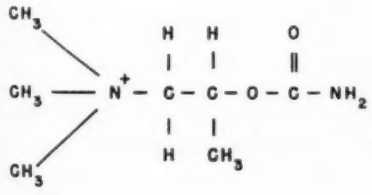
In addition to drugs which resemble acetylcholine, there are also drugs which enhance the effects of acetylcholine by preventing its destruction. These drugs, termed anticholinesterase drugs, include physostigmine and neostigmine (Prostigmine).

FIG. 3

CHEMICAL STRUCTURES OF MECHOLYL AND UROCHOLINE



ACETYL – BETA – METHYLCHOLINE (MECHOLYL)



CARBAMYL – BETA – METHYLCHOLINE (UROCHOLINE)

Ganglionic Blocking Agents. The ganglionic blocking agents are a group of drugs which have been used in a manner similar to that of the cholinergic blocking agents. The first of these were the tetraethylammonium drugs, followed by the pentylmethonium and hexamethonium compounds. Both tetraethylammonium and hexamethonium compounds prevent the stimulating effect of acetylcholine. One sees evidence of widespread ganglionic blockade throughout the body following the administration of these drugs. Dryness of the mouth, blurring of vision, tachycardia, hypotension, dilatation of the stomach with delayed emptying, decreased motility of the stomach, small intestine, colon and bladder, are all usually observed.[11-13] Constipation or even paralytic ileus may result. Inhibition of gastric secretion is likewise common.[14] In gastric or duodenal ulcer tetraethylammonium or hexamethonium often produce prompt relief of pain which coincides exactly with the relaxation and decreased motility[15-17] of the gastrointestinal tract. Since pain produced by distention of the gut, using a balloon, is not relieved by tetraethylammonium it seems likely that relief of pain is not due to blocking the afferent pathway of pain perception.[14]

Cholinergic Blocking Agents. Of all the autonomic acting drugs, the cholinergic blocking agents are of the greatest interest in relation to the gastrointestinal tract. This group of compounds includes a variety of drugs which interfere with the effect of acetylcholine and are therefore depressants of the parasympathetic nervous system. Those previously available include the belladonna alkaloids, particularly atropine and scopolamine. In an attempt to increase the effectiveness of these drugs, synthetic alkaloids have been developed. Most of these compounds resemble atropine, being tertiary amines. Their chief action is a motor depressant one, but if given in sufficient quantity, antisecretory effects may follow.

The most promising development in the field of anticholinergic drugs has been the combination of the amino alcohol ester with the quaternary ammonium structures of tetraethylammonium chloride resulting in a new series of compounds of which Banthine was

the first to be used. These drugs combine the pharmacologic action of both atropine and the tetraethylammonium compounds. Subsequent to the introduction of Banthine, a large number of drugs have been introduced and, indeed, the pharmacologists have succeeded in synthesizing these compounds with greater rapidity than they can be properly evaluated. The major pharmacologic activity of the anticholinergic compounds consists of blocking the nerve impulse transmitted by acetylcholine. Almost all of these drugs, in usual doses, exert their effect at the postganglionic effector site, but if given in higher dosage some degree of ganglionic blockade may be produced.

Classification of Anticholinergic Drugs

The anticholinergic agents can be broken down on the basis of their chemical structure into two large groups, the tertiary amines and the quaternary amines. The tertiary amines include the belladonna alkaloids as well as the newer synthetic tertiary amines. The major pharmacologic development, however, has been in the field of quaternary amines. These drugs will be discussed under three categories: (1) the belladonna alkaloids, (2) the synthetic tertiary amines, and (3) the quaternary amines.

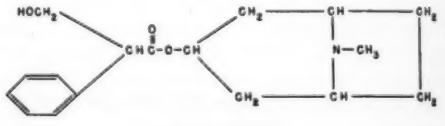
The Belladonna Alkaloids. The principal alkaloids of belladonna consist of atropine, hyoscyamine and scopolamine. Hyoscyamine, the levo-isomer of atropine is more active peripherally than atropine.[18] Scopolamine is closely related to atropine chemically. Its peripheral actions are similar to atropine but centrally its action is antagonistic to atropine.

Despite the widespread use of belladonna alkaloids, there is disagreement as to their pharmacologic action upon the gastrointestinal tract. It is generally accepted, however, that they exert definite depressant effects upon motility. Chapman and associates[19] employed a multiple balloon water manometer system to evaluate the motor depressant effects of the belladonna alkaloids. Oral atropine in dosage of 0.45 to 0.6 mg. or tincture of belladonna 0.4 cc. produced approximately an 80 per cent decrease in both propulsive contractions and total activity of the small bowel. Alterations in tone were less striking. The maximum effect was apparent 75 minutes after administration and lasted about two and a half hours before declining. The motor depressant actions of levorotatory hyoscyamine and scopolamine are similar to those of atropine.[20]

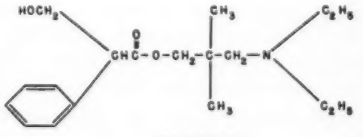
The effect of atropine and the other belladonna alkaloids upon gastric secretion in man is less clear. The normal gastric secretion is not significantly altered by the belladonna drugs in the dosage usually employed.[21] Lockwood and Chamberlain[22] showed that parenteral administration of 0.4 mg. of atropine produced a moderate reduction of acidity and concluded that the secretory depressant action of atropine was in direct relationship to the dose given. Parenteral atropine (1 to 2 mg.) also inhibited the gastric secretory response to histamine and alcohol.[23,24] Levin, Kirsner and Palmer[25] studied the effects of parenteral administration of atropine in dosage of 1 to 6 mg. Variable results upon gastric secretion were obtained. Significant reduction of secretion in all but two instances was accompanied by severe toxic symptoms. They concluded, "therefore, the action of atropine does not

FIG. 4

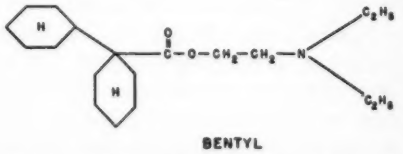
CHEMICAL STRUCTURE OF REPRESENTATIVE TERTIARY AMINES



ATROPINE



SYNTROPAN



BENTYL

(Reprinted from Barborka, C. J., and Texter, E. C., Jr.: Peptic Ulcer—Diagnosis and Treatment, Boston, Little, Brown & Company, p. 140.)

depend upon the dosage or phase activity of the cells when the drug reaches them, but upon the sensitivity of the entire organism to the drug."

Synthetic Tertiary Amines. The earlier pharmacologic work was prompted by the fact that atropine is a tertiary amine. Atropine can inhibit muscle spasm produced by acetylcholine, histamine or barium chloride. However, some of the synthetic drugs are effective only in relieving barium chloride induced spasm. Barium chloride induces spasm of smooth muscle directly regardless of innervation. Drugs which relieve the spasm produced by barium ions but no not affect histamine or acetylcholine induced spasm are called musculotropic spasmolytics. The nitrates and Pavatrine are members of this class. Other drugs which have primarily a musculotropic action are Syntropan and Trasentine. These drugs have little or no antisecretory action, and even in relation to their spasmolytic effect, many are inferior to the action of the natural belladonna alkaloids[19,26-30] (Fig. 4).

Quaternary Amines.

Effect of Quarternization. In most of the newer anticholinergic drugs, the tertiary nitrogen of the compound is quaternized by the formation of a methyl bromide salt or other alkyl- allied salt to form a highly ionized quaternary ammonium ion.[30] This confers upon the compound greater anticholinergic action especially at the ganglion and to some degree at the neuromuscular junction. Quarternization almost eliminates the actions on the central nervous system and local anesthetic actions of most of these compounds. The chemical structure of many of the quaternary amines are quite similar (Fig. 5). Most of these compounds potentially have a dual action: (1) peripheral postganglionic blockade at the effector site, and (2) ganglionic blockade. The postganglionic cholinergic blockade is the most prominent with the doses employed clinically, and higher doses are required before ganglionic blocking activity can be demonstrated.[31,32]

The quaternary amines have little direct relaxing effect upon smooth muscle, but are more active in blocking cholinergically induced activity of the intestine than the tertiary amines. The quaternary amines are less readily absorbed than the tertiary amines with the result that oral toxicity is decreased while intravenous toxicity is increased. A more favorable balance appears to result between gastrointestinal activity and side effects.

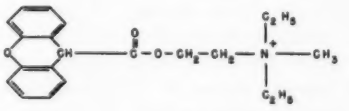
Mechanism of Action. There is a marked similarity in structure between the quaternary amine, anticholinergic drugs, and acetylcholine (Fig. 6). This structural similarity is thought to be related to their mode of action.

Quaternized Derivatives of Belladonna Alkaloids. The quaternary ammonium salt of atropine has been referred to as methyl atropine and has been known as Eumydrin, Metanite, and Metropine. Although this drug has been shown to have both peripheral and ganglionic activity, it has not been widely employed.

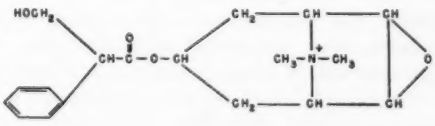
Scopolamine methylbromide (Pamine bromide) has definite anticholinergic activity.[33] Scopolamine n-butyl bromide (Buscopan—SKF 1637) is active following parenteral administration,[32] but the antisecretory activity following oral administration is not very satisfactory.[34]

FIG. 5

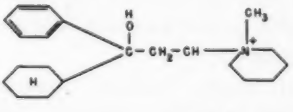
CHEMICAL STRUCTURE OF REPRESENTATIVE QUATERNARY AMINES



BANTHINE



PAMINE

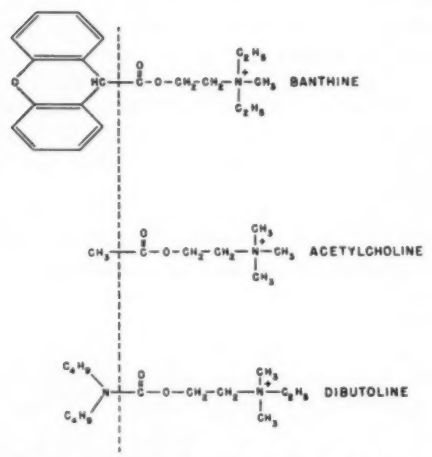


TRICYCLAMOL

(Reprinted from Barborka, C. J., and Texter, E. C., Jr.: Peptic Ulcer—Diagnosis and Treatment, Boston, Little, Brown & Company, p. 141.)

FIG. 6

COMPARATIVE STRUCTURES OF ACETYLCHOLINE, BANTHINE AND DIBUTOLINE



(Reprinted from Barborka, C. J., and Texter, E. C., Jr.: Peptic Ulcer—Diagnosis and Treatment, Boston, Little, Brown & Company, p. 142.)

Homatropine methylbromide (Malcotran and Novatrine) is a quaternary derivative which inhibits both secretion and motility.

Synthetic Quaternary Amines. Methantheline bromide (Banthine) has been studied extensively and has been shown to produce widespread postganglionic blockade of the cholinergic type. In the dosage usually employed, the major action is postganglionic, whereas a considerable increase in dosage is necessary before other actions can be observed. Methantheline inhibits gastric secretion both in normal subjects and in ulcer patients, the antisecretory effect being most consistent after parenteral administration. A depressant effect upon gastrointestinal motility is regularly observed after parenteral administration and often after the oral.[31]

Propantheline bromide (Probanthine) is an analog of Banthine. It has greater anticholinergic activity than Banthine, being active orally in depressing gastric secretion and gastrointestinal motility.[35,36]

Diphenmethanil methyl sulfate (Prantal) and oxyphenonium bromide (Antrenyl bromide) are anticholinergic drugs introduced primarily for the treatment of ulcer.[31,34] Both inhibit gastrointestinal motility but they do not have a consistent antisecretory effect following oral administration.

Pathilon administered parenterally has a profound inhibitory effect upon gastrointestinal motility as well as a consistent antisecretory effect. In the usually employed oral dosage these effects are less consistent.[35]

Darstine inhibits gastric secretion in dogs but clinical studies failed to demonstrate an antisecretory effect when the drug was administered orally in recommended dosage.[31] Monodral depresses basal secretion and gastrointestinal motility.[34]

Tricyclamol is available as tricyclamol chloride (Tricoloid) and tricyclamol sulfate (Elorine sulfate). Both have anticholinergic activity.

Dibutoline (Dibuline) is a choline derivative having anticholinergic activity after parenteral administration, and is of little clinical value.

Benzomethamine chloride (Cotinul) is another quaternary amine which has been shown to have gastric antisecretory activity.

Two piperidol compounds having anticholinergic activity have recently been released. The first of these, n-ethyl-3-piperidyl-dyphenylacetate-hydrochloride (Dactyl), has mainly a motor depressant action.[37] The second is n-ethyl-3-piperidyl-benzylate methobromide (Piptal) which is a quaternized derivative of 3-hydroxypiperadine. Antisecretory activity has been noted,[35,38,39] as well as motor depressant effects. A similar compound, n-methyl-3-piperidyl-benzylate methobromide (JB 340), is also under study particularly in relation to its effect upon colonic motility.

Other new drugs are being studied which are not yet available for clinical usage. One of the most interesting of these is the quaternary amine, 2, 2-diphenyl-4-diisopropylamino butyramide methiodide (SKF 4740J). It is reported to have a duration of action between 8 and 12 hours. Both antisecretory and motor depressant effects have been observed.[40]

(To be continued)

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Thomas Sydenham to Dr. Cole

. . . I have weighed in a nice and scrupulous balance, whether it be better to serve men, or to be praised by them, and I prefer the former. It does more to tranquillize the mind; whereas fame, and the breath of popular applause, is but a bubble, a feather, and a dream. Such wealth as such fame gives, those who have scraped it together, and those who value it highly, are fully free to enjoy, only let them remember, that the mechanical arts (and sometimes the meanest of them) bring greater gains, and make richer heirs. . . .

January 20, 1681.

EDITORIALS

PERICARDITIS: ITS DIAGNOSIS

Other than pericarditis in the late stages of uremia, or associated with the relatively rare invasion of the pericardial sac by a neoplasm, or the pericardial effusion of myxedema,—inflammation of the pericardium was considered generally in past years to be due to one of several infectious agents. Rheumatic pericarditis, a serofibrinous lesion to end in adhesive pericarditis, was recognized as an entity. Similarly, tuberculous pericarditis, also a serofibrinous process, was known to end not infrequently in constrictive pericarditis. Then there were the occasional instances of purulent pericarditis as a complication of septicemia, usually of coccal origin or of some less common organism.

Beginning with World War II there has been an increasing recognition of so-called acute idiopathic, or acute benign, or acute nonsuppurative pericarditis. The characteristic picture is that of a young person, commonly male, who may have had an antecedent respiratory infection and has an abrupt onset of substernal or precordial pain. The pain may radiate to the neck, jaws, shoulders or arm. There is often pain on respiratory movements, and discomfort upon swallowing food may occur. Fever up to 102° or 103° may be present followed by low grade fever for several weeks. A pericardial friction rub usually becomes audible early and lasts several days. Venous distension and a paradoxical pulse may be evident. Upon x-ray examination an enlarged heart shadow is found and pulmonary infiltrations suggestive of pneumonitis. Electrocardiographic changes of pericarditis usually occur.

Another cause of pericarditis, with or without effusion, being recognized with increasing frequency in recent years, is that accompanying disseminated lupus, periarteritis and dermatomyositis. Here again are fever, pain, friction rub, tachycardia and enlargement of the cardiac shadow.

Without question the etiologic diagnosis of pericarditis is frequently wrong, and in the past this was of relatively little moment except in terms of clinical accuracy. With advances in specific treatment of one type or another this attitude cannot be condoned any longer, and the need for accurate etiologic diagnosis has become imperative.

The causes of pain which may be confusing, as angina, spontaneous pneumothorax, pleurisy, hiatus hernia and dissecting aneurysm, can usually be recognized with proper study. Uremia and myxedema also should not give rise to diagnostic difficulties.

Until benign pericarditis was recognized as an entity, the diagnosis of myocardial infarction was made not infrequently in the young man in the armed services early in World War II. Goyette[1] points out that pain on respiration is commonly present in pericarditis, whereas shock, drop in blood pressure and gallop rhythm are not to be expected. Furthermore, a pericardial friction rub within the first 24 hours, and occurring before electrocardiographic changes are strongly in favor of pericarditis and against infarction.[1] He points out the need for accurate diagnosis as between pericarditis and myocardial infarction since anticoagulant therapy is clearly contraindicated in the former because of the serious complications of hemorrhage.

However, the clinician is still left with the problem of a patient with fever and evidence of pericarditis with or without effusion. Does this represent a "collagen disease," a rheumatic infection, a tuberculous infection, a coccal infection, or the viral one of acute benign pericarditis? If of tuberculous origin the patient should plan to give up his occupation for an extended period of time and be treated by bed rest and the exhibition of the chemotherapeutic agents specific for the *Mycobacterium tuberculosis*. If the infective agent is a pyogen, treatment should be with the drug or antibiotic to which it is most sensitive.

The great need for accurate diagnosis points up the shortcomings of the pericardial tap, which most clinicians shun because of technical difficulties if the effusion is small, and because of a fear of puncture of the

1. Goyette, Edwin M.: Acute Idiopathic Pericarditis, Am. Int. Med. 39:1032, 1953.

heart or laceration of the cardiac muscle. These considerations bring to mind biopsy of the pericardium.

Though Goyette and others have done an occasional biopsy, Proudfit and Effler[2] have reported biopsies in 16 patients having pericarditis; 15 of these were living at the time of the report. Though the pericardial fluid was sterile, acid-fast bacilli in one, and *Streptococcus viridans* in another were cultured from biopsy tissue pointing the way to therapy. Chronic hemorrhagic pericarditis was demonstrated in 5 instances and chronic nonspecific pericarditis in 6 patients.

An interesting side light to this subject of biopsy for diagnostic purposes is the treatment of pericarditis by creating a pleuropericardial window. By establishing a communication between these two cavities cardiac tamponade is prevented without resorting to pericardial tap with its dangers of complications. These authors had only one patient in whom fluid from the pericardial sac accumulated so rapidly in the pleural space as to require aspiration from the latter. Generally, such fluid is readily absorbed from the pleural space.

Here then are new thoughts for the clinician. The biopsy of pericardial tissue permits an accurate diagnosis and the possibility of specific therapy as against expensive and time-consuming treatment in the dark. Another thought is the drainage of pericardial effusion from the pericardial sac into the pleural space in the prevention of possible tamponade.

DEATH BY DROWNING

Statistics indicate that over 5,000 deaths by drowning occur annually in this country among the civilian population, and that over half of these take place during the months of June, July and August.

Probably most physicians, if asked to account for death due to submersion, would hold asphyxia and anoxia responsible. A drowning death is due to suffocation and the efforts of resuscitation are the same whether the subject was submerged in salt or in fresh water. However, the physiologic effects of near-drowning are entirely different if the accident occurred in fresh water as compared to that in salt water. Therefore, the aftercare of the survivor depends upon the type of water he aspirated. Shaw[1] has recently reviewed this subject to point out the physiologic alterations in each instance which, thus, lead to rational treatment.

He first considers the physical factors in drowning. Hysterical screaming and struggling may last a minute or two and apparently laryngeal spasm may be so acute as to account for the absence of water in the lungs in some 10 per cent of casualties. In others the spasm leads to swallowing great quantities of water which is then vomited, thereby permitting the aspiration of water into the lungs. In fresh water death by cardiac standstill, or ventricular fibrillation, or convulsions occurs in two to four minutes. In the drowning in salt water the heart's activity may continue for some six or seven minutes.

The author notes that as far back as 1880 it was shown that the blood in the left heart was more dilute in those drowned in fresh water. In 1902, it was recognized that the blood in the left heart was more concentrated if drowning occurred in salt water. But, he indicates, it has been less than ten years since investigators for the Air Force, Swann and his associates, by physiologic and biochemical studies in dogs, have clarified the events which may lead to death in the near-drowned. The proper use of electrolytes to re-establish equilibrium is essential in avoiding late deaths.

Swann's studies show that within three minutes after submersion in fresh water over 70 per cent of body fluid is fresh water, dropping sodium values to as low as 40 mEq./L. and calcium to 2 mEq./L. With hypotonicity hemolysis of red cells occurs freeing potassium which may rise to double its level; potassium intoxication accounts for ventricular fibrillation. By contrast it was shown by experimental work that the aspiration of sea water, because of its hypertonicity, almost instantly causes hemoconcentration, serum sodium rising as high as 250 mEq./L. However, with little change in the sodium to potassium ratio ventricular fibrillation does not occur, and the heart beat continues some six or seven minutes. In both types of immersion plasma proteins diffuse into the alveoli causing pulmonary edema.

2. Proudfit, W. L., and Effler, D. B.: Diagnosis and Treatment of Cardiac Pericarditis by Pericardial Biopsy, J.A.M.A. 161:188, 1956.

1. Shaw, Christopher: On Death by Drowning, Am. Pract. & Digest Treat. 7:776, 1956.

Captain Shaw emphasizes the immediate need for treatment in the form of resuscitation,—to drain the water from the lungs, to clear the air passages and to begin artificial respiration by the Holger Nielson method. He points out that cardiac contractions must return within ten minutes or resuscitation is hopeless.

It is the aftertreatment of the revived victim along rational physiologic lines which may avoid the deaths hours or days later blamed on "exposure" or pneumonia.

In the subject who survived near-drowning in fresh water, a liter of hypertonic saline solution (3 per cent) given slowly intravenously may reverse the hemodilution. It may be repeated in some hours if the serum sodium remains low. Whole blood transfusions alternating with phlebotomy, to reduce the hydremia, may be used. Lower nephron nephrosis may be a complication of the hemolysis.

The hemoconcentration resulting from near-drowning in salt water calls for 5 per cent dextrose in distilled water. The high serum sodium and chlorides interdict the use of blood, serum or normal saline.

Captain Shaw's discussion of the physiologic effects of drowning seems so timely in this season of the year that a detailed review on these pages appeared most appropriate.

THE DISTINGUISHED SERVICE AWARD

The Distinguished Service Award of the Southern Medical Association is the highest honor that can be bestowed upon a member by the Southern Medical Association for meritorious and praiseworthy contributions to Medicine.

The Award was created by an amendment to the Constitution and By-Laws of the Association at the Houston Meeting in 1955. Pursuant to the provisions of this amendment, the Council elected an unpublicized Committee to work out the rules, regulations and mechanics of selecting recipients of the Award.

Since 1912 and until 1955 the Southern Medical Association had awarded a Research Medal. This Medal has been awarded to fifteen distinguished physician-members throughout the South. The Research Medal, however, was awarded only for work done in the field of pure medical research. The limitations of the Research Medal were recognized and a need for an award with a much broader base became apparent. It was for the purpose of broadening the base of the scientific awards of the Association that the Distinguished Service Award was established.

The Distinguished Service Award may be bestowed for outstanding and meritorious work done in *any* field of medicine or its related and ancillary sciences. Thus, outstanding achievement in the fields of medicine, surgery, research, medical education, and in any of the medical and surgical specialties comes within the scope of the Distinguished Service Award.

The Committee, under the instructions of the membership and the Council, established the following rules and regulations regarding the selection of a recipient:

1. Any member of the Association in good standing is eligible for nomination as a recipient of the Award.
2. Any member in good standing of the Association may nominate a recipient for the Award.
3. The nominees are evaluated by an unpublicized Committee which selects three of the nominees annually and submits their names to the Council of the Southern Medical Association.
4. The Council elects annually one of the three submitted by the Committee on the Distinguished Service Award as the recipient.
5. The election by the Council is held during the Annual Meeting of the Association. If possible, the winner is publicly presented to the Association during the last general session of the membership at a given annual meeting.

In addition to the rules and regulations governing the selection of the recipient, the Committee established certain mechanics and devised official forms for placing physician members in nomination.

These official forms are available from the Executive Secretary of the Association. Any member of the Association desiring to place a fellow physician-member in nomination may secure an official form from the headquarters office.

These forms provide for:

1. Biographical information on the nominee, including a recent photograph, if available
2. Medical education and training of the nominee
3. A professional history, including private practice, specialty training, contributions to medical literature, teaching affiliations, staff connections, etc.
4. A detailed description of a specific or general contribution or accomplishment of the nominee to the advancement of Medicine or any of its

phases upon which the nomination is to be based

5. Submitting substantiating evidence of merit, including printed materials, publications, articles, other citations, etc.

The completed forms should be mailed to the Executive Secretary of the Association, Room 1020, Empire Building, Birmingham 3, Alabama, and no nomination can be processed without the completion of all proper forms.

After the nominations are received in the headquarters office, reproduced copies will be mailed to the members of the unpublicized Committee on the Distinguished Service Award. The Committee, composed of five members with staggered terms of office, will select three of the nominees and submit their names to the Council.

The Council is required to elect a recipient from among these three nominations at its first session at a given annual meeting. The elected recipient will be notified of his election and he should appear, if possible, in person for public recognition and shall receive the award at the last general session of the Annual Meeting.

Because of the enormous contributions to medicine in the South for the past fifty years, it is most fitting that the first Distinguished Service Award be given at the Golden Anniversary Meeting of the Southern Medical Association in Washington on November 12-15, 1956.

Undoubtedly, the Distinguished Service Award of the Southern Medical Association will not only represent the top honor for men of medicine in the South, but indeed will be held in comparable esteem with other notable awards.

25 YEARS AGO

Arterial Encephalography in Brain Tumors*

"The first study of arterial encephalography dates back to 1927. In that year, Moniz read a paper on the subject before the Society for Neurology and Academy of Medicine in Paris.

"Since then we have been quite uniformly successful in localizing brain tumors by the method, which consists, briefly, in injecting into the internal carotids an opaque liquid which renders impervious to the x-ray the whole system of brain arteries. The alterations in the arterial system produced by the tumors are a means of locating the latter. An encephalographic study is easily made and the method may be used in any patient suspected of having a brain tumor. . . .

"The opaque liquid used is a chemically pure, recently prepared, watery (22 to 25 per cent) solution of iodide of sodium. As this solution is quickly diluted by the blood and thus ceases to possess the indispensable quality of opacity under the x-rays, it is necessary to photograph the head immediately after the injection and to use a sufficiently quick apparatus.

"It is advisable to give the patient 30 centigrams of Luminal, both the night before and early on the day of examination. We have thus frequently avoided . . . epileptic attacks which may follow the injection. Such attacks in our experience have usually been homolateral and have been of the Jacksonian type. . . .

"As it is impossible to make the injection direct, it is necessary first to expose the carotids. . . . we made the injection into the common carotid, temporarily obliterating the external carotid. . . .

"The patient is placed in the required position under an x-ray bulb, that is he lies on the side opposite that to be injected, ... As soon as the attendant gives the signal that the apparatus is ready to use the artery is punctured by means of the needle. . . . It has been our custom, when making the puncture in the common carotid, to introduce the needle far enough to enter the internal carotid. In this way the injection is made just as though it had been started directly in the latter. . . . At present we prefer to inject 6 or 7 cubic centimeters—a little less in the case of women—and we use 2 to 3 cubic centimeters in children. It is essential that the injection be made very quickly and that the radiogram be made at the very moment at which the quantity injected seems to be sufficient.

"We have made approximately 200 encephalograms in 100 patients with this method, and we may say that except in the presence of arteriosclerosis and in instances in which we used an iodide solution not sufficiently pure, we have experienced no difficulties. We have thus succeeded in localizing brain tumors either by rendering visible the accessory circulation of the tumors or the dislocation of the arteries. We present brief histories of a few of our cases.

Summary of Observations

"When we began our studies in arterial encephalography, we gave special attention to the dislocation of the sylvian group as we believed they were es-

*Moniz, E., Pinto, A., and Lima, A.: Arterial Encephalography and Its Value in the Diagnosis of Brain Tumors, Surg., Gynec. & Obst. 53:155, 1931.

pecially capable of revealing the existence of a subjacent tumor. And this for two reasons: (1) the sylvian group is constantly visible, normally showing the same direction and similarity of constitution; (2) the first arteriograms made did not reveal any of the aspects later discovered in the course of our experiments, namely: visibility of the adventitious circulation of some tumors and visibility, in certain cases, of the anterior cerebral artery and its ramifications.

"In the dislocation of the sylvian group we have been able, so far, to locate and make accurate diagnoses in 18 cases of brain tumors, and of these 14 were confirmed by the operation, the four remaining not having been operated upon. The direct visibility of the arteries was observed in 13 cases; of these, nine were operated upon. . . .

"When there is a tumor of certain volume in one of the brain halves, it is sometimes possible to see the anterior cerebral artery on the opposite side. Through compression the tumor prevents the regular circulation and the anterior communicating vessel ceases to take the blood from the compromised half of the brain to the opposite side because of the diminution in pressure in the anterior cerebral artery of that side. . . .

" . . . After prolonged observations, we came to the conclusion that considerable dilatation of the ventricle or the presence of a tumor compressing the anterior communicating artery, apart from the two anterior cerebral arteries, rendering it difficult for the blood to pass from one to the other owing to the stretched and decreased size of the communicating artery, must be the reason of the visibility of the two anterior cerebral arteries. Tumors of the central region of the brain, for instance of the third ventricle, of the pineal region, and of the quadrigeminal tubercles must fall in this class. . . .

"The importance of this new interpretation of arteriograms seems to us to be of the utmost importance inasmuch as tumors of the central regions offer, as a rule, very deficient clinical symptomatology."

BOOK REVIEWS

Textbook of Endocrinology

Edited by Robert H. Williams, Executive Officer and Professor of Medicine, University of Washington Medical School, Seattle. 776 pages, 175 figures. Second Edition. Philadelphia: W. B. Saunders Company, 1955. Price $13.00.

This textbook of endocrinology is a well-knit product of the twelve investigators who have combined their individual interests and information of special phases of endocrinology. Their observations have been coordinated by the skillful pen of Robert Williams into an outstanding textbook. There are chapters on the general physiology of the endocrines, laboratory diagnostic and assay procedures and on the treatment of endocrine disorders. Special attention is given to the brands and amounts of medication suggested for these various conditions. There are special chapters devoted to the pituitary, thyroid, adrenals, testes, ovaries, pancreas, and the parathyroid glands. A special chapter discusses the influence of the endocrine glands upon growth and development, one is devoted to neuro-endocrinology, and one chapter is given to the problem of obesity.

The format and printing is excellent. The paper gives a helpful background to the well-printed contents. The illustrations are numerous and, except for poor x-ray reproductions, are well done and to the point.

There is a wealth of information in the various chapters, the bibliographies are full and specific.

The first edition of this book was published in 1950. The contributors to the second edition are the same, except that the chapter on the adrenals formerly edited by the late Dr. Kepler has been written, and well, by Forsham and Thorn, and the subject of obesity, ably presented by W. H. Daughaday instead of L. H. Newburgh.

The chapter on diseases of the parathyroid glands is the lengthiest and the chapter on neuro-endocrinology is somewhat polysyllabic.

Dr. Williams can take pride in having accomplished the difficult feat of presenting the essential aspects of the field of endocrinology into a single and not laborious text. He has done a masterful job of making the problem simple enough for the uninitiated and detailed enough for the more mature student of endocrinology. Certainly this outstanding textbook should be a valued possession on the reading shelf of any student, teacher or practitioner, who is curious relative to the problems in glandular disorders.

Systemic Lupus Erythematosus

By A. McGehee Harvey, M.D., Lawrence E. Shulman, M.D., Philip A. Tumulty, M.D., C. Lockard Conley, M.D., and Edyth H. Schoenrich, M.D., from the Department of Medicine of the Johns Hopkins University and Hospital. 136 pages. Baltimore: Williams and Wilkins Company, 1955. Price $3.00.

The increasing interest in the so-called collagen diseases as shown by a rapidly expanding literature makes this latest review of the literature a valuable contribution in the field.

This book is a reprint of a review of the literature and an analysis of 138 cases of systemic lupus by the authors from the material at Johns Hopkins Hos-

Continued on page 928

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BOOKS RECEIVED

Diseases of the Skin. By Richard L. Sutton, Jr., M.D., Chairman of the Department of Dermatology, University of Kansas Medical Center. Eleventh edition, 1441 pages, with 1972 illustrations. St. Louis: The C. V. Mosby Company, 1956. Price $29.50.

Techniques and Procedures of Anesthesia. By John Adriani, M.D., Director, Department of Anesthesiology, Charity Hospital; Professor of Surgery, Tulane University School of Medicine; and Clinical Professor of Surgery and Pharmacology, Louisiana State University School of Medicine, Second Edition, 538 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $8.75.

Diseases of the Nose, Throat and Ear. By I. Simson Hall, M.B., Ch.B., F.R.C.P.E., F.R.C.S.E., Surgeon to the Royal Infirmary, and Lecturer in Diseases of Nose, Throat and Ear at University of Edinburgh. 448 pages, Sixth Edition, illustrated. Baltimore: The Williams & Wilkins Co., 1956. Price $4.75.

Poliomyelitis. By W. Ritchie Russell, C.B.E., M.D. (Edin.), D.Sc. (Oxon.), F.R.C.P. (Edin.), F.R.C.P. (Lond.), Director, Department of Neurology, United Oxford Hospitals and Clinical Lecturer in Neurology, University of Oxford. Second Edition, 143 pages. Baltimore: The Williams & Wilkins Co., 1956. Price $3.00.

Surgery of the Eye—Diseases. By Alston Callahan, M.D., Birmingham, Ala. 425 pages, illustrated. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $25.00.

Cytology of the Blood and Blood-Forming Organs. By Marcel Bessis, Director of Research Laboratory, Centre National de Transfusion Sanquine, Paris. Translated by Eric Ponder, The Nassau Hospital, Mineola, New York. 622 pages, illustrated. New York: Grune & Stratton, 1956. Price $22.00.

Histamine. Ciba Foundation Symposium jointly with The Physiological Society and The British Pharmacological Society. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Cecilia M. O'Connor, B.Sc. 460 pages, 133 illustrations. Boston: Little, Brown and Company, 1956. Price $9.00.

Understanding Human Behavior. By James L. McCartner, M.D., 235 pages. New York: Vantage Press, 1956. Price $3.50.

Mental Health Planning for Social Action. By George S. Stevenson, M.D., National and International Consultant, The National Association for Mental Health, Inc. Consultant to U. S. Public Health Service, Department of Health, Education and Welfare. 340 pages. New York: The Blakiston Division of McGraw-Hill Book Company, Inc., 1956. Price $6.50.

An Atlas of Regional Dermatology. By G. H. Percival, M.D., Ph.D., F.R.C.P.E., D.P.H. Grant Professor of Dermatology, University of Edinburgh; and T. C. Dodds, F.I.M.L.T., R.I.B.P., F.R.P.S. 256 pages, containing 475 Clinical subjects in full color. Baltimore: The Williams and Wilkins Company, 1955. Price $19.00.

Synopsis of Gynecology. By Robert James Crossen, M.D., Associate Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine. Fourth edition, 245 pages, 132 illustrations. St. Louis: The C. V. Mosby Company, 1956. Price $5.25.

Gynecologic Nursing. By Robert James Crossen, M.D., Associate Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, St. Louis, and Ann Jones Campbell, R.N., Director of Barnes Hospital School of Nursing. Fifth edition, 260 pages, with 171 illustrations, including three in color. St. Louis: The C. V. Mosby Company, 1956. Price $4.25.

Mosby's Review of Practical Nursing. Edited by Dorothy Kelley Rapier, R.N., Marianna Jones Koch, R.N., and Deborah MacLurg Jensen, R.N. 322 pages, illustrated. St. Louis: The C. V. Mosby Company, 1956. Price $4.25.

Progress in Hematology. Edited by Leandro M. Tocantins, M.D., with 27 contributors. 329 pages. New York: Grune and Stratton, 1956. Price $9.75.

Microbiology and Pathology. By Charles F. Carter, M.D., Director, Carter's Clinical Laboratory, Dallas, Texas, and Alice Lorraine Smith, M.D., Assistant Professor of Pathology, Baylor University College of Medicine. Sixth edition, 931 pages with 313 illustrations. St. Louis: The C. V. Mosby Company, 1956. Price $6.50.

Nurse-Patient Relationships in a Hospital Maternity Service. By Marion S. Lesser, M.A., Director, Special Study in Obstetric Nursing Service, Women's Clinic, The New York Hospital, and Vera R. Keane, B.S., R.N., Instructor-Supervisor in Obstetric and Gynecologic Nursing, Cornell University, New York Hospital School of Nursing. 301 pages. St. Louis: The C. V. Mosby Company, 1956. Price $4.25.

Composting. Sanitary Disposal and Reclamation of Organic Wastes. By Harold B. Gotaas, Professor of Sanitary Engineering, Department of Engineering, University of California. World Health Organization: Monograph Series No. 31. 205 pages, 49 figures. Geneva, 1956. New York: Columbia University Press, International Documents Service. Price $5.00.

Physical Diagnosis. By Ralph H. Major, M.D., Professor of Medicine, and Mahlon H. Delp, M.D., Professor of Medicine, both of the University of Kansas. Fifth edition, 328 pages, 536 figures. Philadelphia: W. B. Saunders Company, 1956. Price $7.00.

The Morphology of Human Blood Cells. By L. W. Diggs, M.D., Professor of Medicine and Director of Medical Laboratories, University of Tennessee and City of Memphis Hospitals; Dorothy Sturm, Instructor, Memphis Academy of Arts; and Ann Bell, B.A., Instructor in Medicine, University of Tennessee. 181 pages, 31 color plates, 54 figures. Philadelphia: W. B. Saunders Company, 1956. Price $12.00.

Endogenous Uveitis. By Alan C. Woods, M.D., Professor Emeritus of Ophthalmology, the Johns Hopkins University School of Medicine. 293 pages, illustrated. Baltimore: The Williams and Wilkins Company, 1956. Price $12.50.

Biochemistry of the Eye. By Antoinette Pirie, M.A., Ph.D., Margaret Ogilvie's Reader in Ophthalmology, University of Oxford, and Ruth van Heyningen, M.A., D.Phil., Nuffield Laboratory of Ophthalmology, University of Oxford. 316 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $7.00.

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Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Footnotes and bibliographies should conform to the following style:

1. Doe, J. E.: What You Should Know about It, New England J. Med. 243:435, 1950.

Illustrations: Black and white glossy prints, preferably 5 by 7 inches, and drawings in India ink on white paper are required. The author's name, number and indication of top, if doubtful, should be attached. Necessary plates not exceeding six, or one and a half pages, will be furnished by the Journal.

Reprints: Reprints are available at publisher's cost. An order form will accompany author's galley proof and should be returned with the galley to the Editor.

Book Reviews: Books and monographs submitted for review should be mailed to the Editor. Acknowledgment will appear in the Journal. Selection rights reserved.

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Business Address: All correspondence related to membership, subscriptions, advertising, and other business should be addressed to the Southern Medical Association, Empire Building, Birmingham 3, Alabama.

SOUTHERN MEDICAL NEWS

ALABAMA

Dr. John A. Martin, Montgomery, has been named president-elect of the Medical Association of the State of Alabama. The new vice-presidents are Drs. W. R. Carter, Repton, Hugh Gray, Anniston, S. W. Windham, Dothan, and W. D. Anderson, Tuscaloosa. Dr. Douglas L. Cannon, Montgomery, will serve as secretary-treasurer.

Drs. W. C. Simpson, Florence, William C. Hannon, Mobile, and James O. Morgan, Gadsden, were re-elected to serve a five-year term on the Physicians' Advisory Board to the University of Alabama.

The new science hall at Jacksonville State College has been dedicated in memory of Dr. Thomas Wilburn Ayers, who died in 1954. He and his brother-in-law, the late Dr. John C. LeGrande, founded the *Alabama Medical Journal* and Dr. Ayers was its first editor.

Dr. Arthur H. Mountford, Tuscaloosa, has retired after 32 years of service with the Veterans Administration and as manager of the Veterans Administration hospital. Dr. and Mrs. Mountford were honored at a tea and presented gifts for their new home.

ARKANSAS

Dr. T. Duel Brown has been elected president of the Urological Section of the Arkansas Medical Society. Drs. Grady Reagan and Ralph Down will serve as vice-president and secretary-treasurer respectively.

The 50-Year Club has elected the following officers: Dr. W. E. Hamil, Pocahontas, president; Dr. J. C. Gilliam, Des Arc, vice-president; and Dr. John H. McCurry, Cash, life secretary.

An Arkansas Chapter of the American Trudeau Society has recently been formed. Dr. Fred Gray, Little Rock, was elected president. Dr. Harley Darnall, Ft. Smith, is president-elect and Dr. W. E. Morris, Little Rock, will serve as secretary-treasurer.

Dr. George W. Rodkey, formerly medical director of Firland Sanatorium in Seattle, Washington, has assumed the duties of head of the hospital medical staff at State Sanatorium of Arkansas.

Dr. Anderson Nettleship has resigned as head of the department of pathology of the University of Arkansas School of Medicine and as state medical examiner. He will continue as professor of pathology at the University.

Dr. John C. Wright, formerly of Water Valley, Mississippi, has become associated with the staff of the Harris Hospital and Clinic in Newport.

DISTRICT OF COLUMBIA

Dr. Ralph M. Caulk, has succeeded Dr. W. Ross Morris, as president of the Medical Society of the District of Columbia. The other new officers are: Drs. James W. Watts, president-elect; Irving Burka, first vice-president; Shirley Martin, second vice-president; W. Ross Morris, member of the Executive Board; and W. Leroy Dunn, member of the Board of Censors.

Drs. Raymond T. Holden and Herbert S. Gates will serve as delegate and alternate delegate to the American Medical Association.

Dr. William H. Delvin has been elected president of the Section on Anesthesiology of the Medical Society of the District of Columbia and the District of Columbia Society of Anesthesiologists. Dr. William E. Bageant is the new vice-president and president-elect. Dr. Arch S. Russell, Jr., has assumed the duties of secretary-treasurer.

The newly formed Section on Internal Medicine and Allied Subspecialties has named the following officers: Dr. Henry D. Ecker, chairman; Dr. Benjamin Manchester, vice-chairman; and Dr. William K. Billingsley, Jr., secretary-treasurer.

The Georgetown Clinical Society has elected Dr. Raymond A. Osbourn, president, Dr. Philip Burka, vice-president, and Dr. Paul F. Jaquet, secretary-treasurer, for the coming year.

On April 27, the Mid-Atlantic Chapter of the American Medical Writers' Association was organized. The officers are: Dr. I. Phillips Frohman, president; Dr. Robert P. Oldenwald, vice-president; and Dr. W. Calhoun Stirling, treasurer.

Dr. Crenshaw D. Briggs has succeeded Dr. John Hugh Lyons as chief of the surgical department of Emergency Hospital. Dr. Theodore J. Abernethy was appointed chief of the medical department, succeeding Dr. John Minor. Dr. Lyons and Dr. Minor were named Emeritus Chief and Senior Consultant of the Departments of Surgery and Medicine, respectively. The medical staff has elected the following officers: Dr. John A. Reisinger, president; Dr. Walter A. Atkinson, first vice-president; Dr. R. Bretney Miller, second vice-president; and Dr. E. Herbert Bauersfeld, secretary.

Dr. Wallace M. Yater has been elected secretary general of the American College of Physicians.

Dr. Jacob J. Weinstein, associate in surgery, George Washington University School of Medicine, has been chosen president-elect of the International Academy of Proctology.

Dr. Ellis April, an allergist on the staff of Georgetown University School of Medicine, has been appointed a consultant to the Council on Pharmacology and Chemistry of the American Medical Association.

Dr. Benedict J. Duffy, Jr., director of the Isotope Laboratory and assistant professor of medicine, Georgetown University School of Medicine, presented a paper at the Hawaiian Centennial Medical Meeting in Honolulu.

Dr. Robert J. Coffey, professor and director of surgery, and Dr. Charles A. Hufnagel, professor of experimental surgery, and director of the surgical experimental laboratory, both of Georgetown University School of Medicine, have been named to membership in the American Surgical Association.

Dr. Peter D. Comanduras, associate clinical professor

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*New Officer—Elected Houston Meeting, 1955

BOOK REVIEWS

Continued from page 922

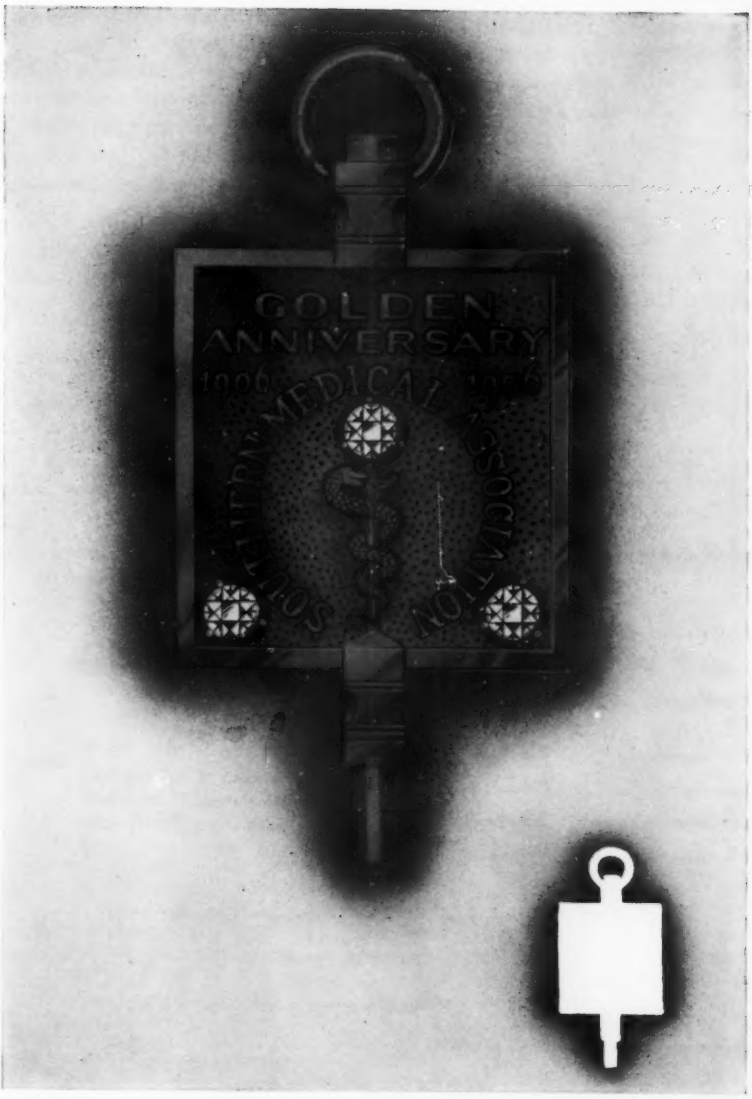
pital. The paper originally appeared in December, 1954, in *Medicine*. This reprint in book form will make this valuable contribution available to many more than the limited number of subscribers to *Medicine*. In this review the authors discuss in detail many aspects of systemic lupus in terms of pathology, etiology and pathogenesis as well as the varied clinical picture with manifestations in all systems of the body. Excellent consideration is given to the hematologic phenomena including the L.E. cell, abnormalities of the serum proteins, and the false biologic tests for syphilis. So too, the review is excellent insofar as our present knowledge is concerned concerning the management and prognosis in these cases.

To the reader who has been attempting to keep his thinking straight in the rapidly expanding literature on the subject of lupus erythematosus disseminata, this review and clinical study will bring him up to date at least as of 1955.

The Hemorrhagic Disorders

By Mario Stefanini, M.D., Associate Professor of Medicine, Tufts University School of Medicine, and William Dameshek, M.D., Professor of Medicine, Tufts University School of Medicine. 368 pages, illustrated. New York: Grune and Stratton, 1955. Price $11.75.

It might be seriously questioned whether the publication of still another book on hemorrhagic diseases is a good thing at this time. Nevertheless, the reviewer's impression is that this is a distinctly worthwhile production. Most of the current treatises on this subject have been written by biochemists, physiologists, and pathologists with seemingly undue emphasis on disorders of the coagulation mechanism to the neglect of disturbances in vascular and platelet factors. Ill-defined though they may be and certainly less readily subject to laboratory evaluation, hemostatic disturbances due to vascular dysfunction nevertheless frequently present a problem to the clinician. One distinct advantage of this book is that the authors are clinicians as well as clinical investigators and have employed a reasonably practical approach with lab-



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oratory studies representing but one phase in the management of the patient. In short this book can definitely be "clinically useful."

The material is well organized. The style of writing is quite unencumbered and readable. The many excellent figures and plates undoubtedly determined the comparatively great cost for a relatively small book. It is obviously difficult to collect a reasonably comprehensive bibliography in the field of hemorrhagic disorders. With few exceptions or omissions this bibliography is well chosen. The problem of writing a book, truly current in a field with such active investigation, is underlined by the fact that the authors found it necessary to add a considerable addendum concerning studies documented after "going to press."

The chief criticism of this book is that frequently very attractive theoretical considerations have led the authors to conclusions which are somewhat dubious and which would be seriously questioned by many other investigators. In all fairness, perhaps this is a necessary sacrifice attendant upon writing a "practical book." However, temporary expediency strictly for attractive theoretical considerations may only eventually compound confusion. Such has all too often been the history of the development of thought in the field of hemorrhagic disorders. The reviewer would certainly question the significance attributed to the increased fibrinolytic activity detectable in some cases of so-called "fibrinolytic purpura" as well as the significance attributed to serotonin deficiency in certain hemorrhagic states. The faith placed in the reliability of current tests to demonstrate so-called platelet agglutinins *in vitro* would likely not be shared by many other investigators. Certainly others have not experienced the degree of success that the authors imply with the use of steroid hormones in hemorrhagic diseases in general.

There is an excellent appendix on technics employed in the study of hemorrhagic disorders. There is perhaps no other field in medical investigation in which the use of technical appendices or manuals in a routine or "cookbook" manner has led to such great confusion. This book contains insufficient warning that these tests must be rigidly and repeatedly standardized on normal subjects by the laboratory personnel who will run the tests and in the environment in which the determinations will be carried out.

The above criticisms are presented because this excellent book will likely become a bible for many clinicians. With these reservations in mind this book can be said to fulfill a real need and to be a fine production. It is difficult to recommend another expensive book for general purchase and use. Nevertheless, the clinician should at least know of its availability. To the student of the particular field this book is a must, even if only for ready reference and bibliography.

Peptic Ulcer

By Clifford J. Barborka, M.D., Associate Professor of Medicine and Chief, Gastrointestinal Clinics, Northwestern University Medical School; and E. Clinton Texter, Jr., M.D., Associate in Medicine and Assistant Chief, Gastrointestinal Clinics, Northwestern University Medical School. 290 pages, 33 illustrations. Boston: Little, Brown and Company, 1955. Price $7.00.

The coverage given the subject of peptic ulcer is sufficiently complete, yet not ponderous to the point of belaboring the busy practitioner. The organization is such that the reader may, on brief reading, review all currently existing concepts regarding etiology and pathogenesis. Reference to the experimental work is frequent, well summarized, and well documented. The anatomy and physiology is offered in an elementary fashion with little effort toward minute detail. A particularly good section pertains to the treatment of peptic ulcer. The section on medical treatment evaluates the various therapeutic agents currently employed, clear evaluations of the tertiary amine and the "why" of their replacement by the quaternary amines in the scope of treatment is explained. The authors offer to the busy practitioner a very useful point in their evaluation, by trade name, of the presently employed proprietary drugs. Antiacid medications are handled similarly.

The sections on clinical management allow for a complete coverage with minimum verbosity. Various locations of ulcers (i.e., esophageal, gastric, duodenal, etc.) are handled individually as to symptoms and treatment, with particular reference to dangers paramount to certain gastric ulcerations. A section is devoted to complications and their management. The section referable to surgical treatment is brief, but indications for surgery are presented didatically.

In general, the book offers a clear and concise accumulation of most of the important points both clinical and experimental relative to the understanding and management of peptic ulcer. Its tone is directed primarily at the busy practitioner who wishes accurate and complete information or review with minimal time expenditure.

Suprapubic Prostatectomy

By Univ. Prof. Dr. Theodor Hryntschak, Late Director, Urologischen Abteilung der Wiener Stadtischen Allgemeneinen Poliklinik. Authorized translation by Noble S. R. Maluf, M.D., Assistant Professor of Urology, Baylor University College of Medicine, Houston. 187 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $8.50.

This monograph presents a detailed report of 100 cases in which the author utilizes his new technic for performing suprapubic prostatectomy. His thoughts concerning preparation, postoperative care, and complications accompany the description of the method.

Suprapubic prostatectomy as now generally performed is virtually the same as when first described over 60 years ago. The same bugaboos plague surgeons now as then,—inadequate hemostasis and poor wound healing because of necessity for suprapubic catheter. Prof. Hryntschak revives and modifies a method propounded by Harris, an Australian urologist, in 1934. The primary differences from the usual technic consist of a blunt transverse bladder incision, transverse sutures re-approximating the anterior portion of the internal vesical orifice for hemostasis, purse-string suture for bladder closure without suprapubic catheter, and finally removal of the urethral catheter from 1 to 3 days postoperatively.

The results obtained by this method compare rather favorably with those by other technics and routes. The mortality rate of 4 per cent would be higher than many series.

The method as described would elevate suprapubic prostatectomy as a surgical procedure from blind surgery to "not-quite-so-blind."

Induced Abortion on Psychiatric Grounds; A Follow-up Study of 479 Women

By Martin Ekblad. 237 pages with tables. Norregade 6—Copenhagen: Ejnar Munksgaard, 1955.

The monograph presents a psychiatric analysis of 479 patients followed by the author after legal abortions granted under the Swedish Abortion Act of 1946. This act legalized abortion on medical, medical-social, social-medical, humanitarian and eugenic indications. In 1951, 6,328 were done which constituted 57.7 legal abortions to every 1,000 children born alive.

The majority of the women had been followed more than three years since the operation. The examination included a psychiatric exploration and an intelligence test, as well as a careful review of their case histories and social conditions. The intellectual level of the examined women was, on an average, lower than the calculated level for the average population, but not lower than the level in a group of women of the same social origin not applying for abortion. As many as 58 per cent of the women had manifested symptoms of chronic neuroses or abnormal personality before the pregnancy in question.

The causes of a woman's coming to need legal abortion on psychiatric indications are discussed, and the distribution according to the different legal indications is indicated. Nearly 80 per cent of the abortions were granted on the indication "emotional weakness." None of the women were psychotic.

The possibility of illegal abortion and suicide in the event of the woman's being refused legal abortion is considered. The results indicate that a large number of women who were granted legal abortion on psychiatric indications would have given birth to the child if this possibility had not been available. The risk of suicide in the event of the refusal of an application for legal abortion is greatest for the women who have been deserted by the male partner. This applies especially to the unmarried women; and in this group, the greatest reduction in the instance of illegal abortion occurs.

It is interesting to note that 37 of the married women soon became pregnant after the abortion and carried their children through to term and made no application for legal abortion. Their reason for this, in the majority of cases, was a sense of guilt over the previous abortion. Legal abortion entails feelings of guilt and self-reproach in many women. The author shows that the greater the psychiatric indications for a legal abortion, the greater the risk is of unfavorable psychic sequelae after the operation; and in these cases, sterilization leads to a better prognosis.

The Sterilization Act of 1941 in Sweden allowed sterilization on eugenic, social-medical, and medical-social indications. The latter mentioned indication refers to "weakness" in the woman and applies, as in the Abortion Act, to so-called "worn out mothers." There were no serious psychic sequelae in the group of women sterilized at the time of abortion. It is interesting that there were only 52 of these; the indications for sterilization being far more stringent than that for abortion.

In summary, the book presents a detailed description and history of the Swedish Abortion Act and case psychiatric follow-ups on 479 women examined by the author. Since our laws and customs differ so greatly from the Swedish, the book is of value to us only in studying the long-term emotional reaction in cases of induced abortion.

Gestation

Transactions of the First Conference March 9-11, 1954, Princeton, N. J. Edited by Louis B. Flexner, M.D., Professor and Chairman, Department of Anatomy, University of Pennsylvania School of Medicine, Philadelphia. 238 pages. New York: Josiah Macy, Jr. Foundation, 1955. Price $5.00.

The monograph deals with three areas of investigative studies of placental function,—the functional role of the placenta, problems of sugar transport in the placenta of the Ungulata, and the comparative anatomy and histology of the placental barrier. These were the topics thoroughly discussed at the first conference on Gestation sponsored by the Josiah Macy, Jr. Foundation.

The participants are the elite of their field in this country and England. To say that each subject was discussed would be a misnomer; they were dissected under microscopy. Formal papers are lacking, and as a result, the unfamiliar will have some difficulty in following continuity. The discussion ranged far and wide around the topics, and revealed healthy differences of interpretation of results. In essence, the discussion revolved about mineral transfer, glucose and fructose metabolism and the trophoblastic structure, and comparative anatomy of the placenta. A great deal of the basic work has been done in lower vertebrates, but human comparisons are multiple.

This monograph will be of most value to those interested in the field, and may stimulate the novice to additional basic reading on the complex mechanism and metabolism of the placenta.

Physicians' Office Attendants Manual

By Henry B. Gotten, M.D., Associate Professor of Medicine, and Douglas H. Sprunt, M.D., Professor of Pathology, University of Tennessee College of Medicine. 90 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $3.75.

This handbook was prepared at the University of Tennessee for the training of medical assistants, secretaries, and office attendants, who are not technicians.

The book is divided into two sections. The first part deals with the subject of office work. In it are discussed the keeping of records, stenographic work, bookkeeping, telephone calls, referrals, hospital consultations, care of supplies and assistance in the treatment room. The second part of the book concerns

laboratory technics. It is the opinion of the reviewer that this is an excellent book dealing with the fundamentals in office procedure. It has the advantages of being informative, brief, and the material is presented simply.

Should the Patient Know the Truth?

Edited by Samuel Standard, M.D., and Helmuth Nathan, M.D. 160 pages. New York: Springer Publishing Company, Inc., 1955. Price $3.00 for hard cover, $2.00 for soft cover.

This book approaches the ever present "doctor's dilemma" in a very refreshing way. Twenty-four authors, including doctors, nurses, clergymen, and lawyers, contribute individual thinking and experiences relative to actual problems. By virtue of this multiple authorship no concerted effort is made to tell the physician what is right or wrong. A theme permeates most of the writings, however, and this is the importance of the patient-doctor relationship. As all will agree, the patient's well-being is of first consideration. This book can help significantly in assisting the physician to see his patient clearly, with as much freedom from projection as possible and yet with intense understanding which is not overbearing. In such a situation the answer to the problem may be found.

One cannot fail to realize after reading this collection of opinions that there is considerably more to the problem than was first anticipated. The book's print and organization make for easy reading. The material draws heavily on patient experience. On finishing, the average reader will feel considerably better prepared to meet the problem the next time it arises.

Medical Problems of Old Age

By A. N. Exton-Smith, M.A., M.D., M.R.C.P. 331 pages. Baltimore: The Williams and Wilkins Company, 1955. Price $7.00.

This book, the first of its kind published in England, might be considered a textbook of geriatrics. Subject matter, however, is based primarily on the author's experience, though this experience appears to be ample. Organization is such that ready reference is difficult,—the greatest value being in the offering of general principles of the various aspects of the care of the aged. The author cleverly provokes thought as to what may be considered "health" in the aged, bringing out the point that the dividing line of normal and abnormal is considerably more variable and more poorly defined in the aged.

Clinical implications of aging are well discussed with special emphasis that aging may progress at varying rates in different systems as well as within one system. It is brought out that the variations in individuals is increased by aging, and most important that the response of the aged to disease may be deceivingly different. A striking poverty of both local and constitutional response to infection and trauma may be encountered in this age group which could well lead to dangerously tardy or erroneous diagnosis.

In addition to the clinical implications of aging, the book competently discusses maintenance of health, practical considerations in home care, and rehabilitation,—a most important component in which the physician with specific knowledge may be of great value. Surgery and anesthesia is handled superficially, and insufficient effort is devoted to the section on mental disorders of the aged. An effort is made to discuss disorders on a system basis, showing the contrast of responses in the aged and pregeriatric group. A point is made that in the geriatric age it is the exception rather than the rule to find the patient suffering from only one disorder or disease. Specific problems such as fecal impaction, incontinence and retention of urine, and so forth, frequently encountered in the care of elderly patients are emphatically recounted. The relatively obvious point of the need for an understanding of the whole is brought out in such examples as the development of urinary difficulties at an earlier stage in the treatment of conditions requiring hypotensives. A very important point discussed somewhat briefly was that many of the real problems specific to geriatrics might well have been obtunded had preparations begun some twenty to thirty years previously.

This book cannot but help to give a greater insight into the problems of geriatric patient care. With ever increasing volume of people in this group this knowledge should be a requirement of almost every specialty as well as, more importantly, of general practice and internal medicine.

Salivary Gland Tumors

By Donald E. Ross, M.D., Chief Surgeon, Ross-Loos Medical Group, Los Angeles. 86 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $7.50.

The author sets for himself the task of clarifying the origin and pathology of salivary gland tumors. In addition, he desires to present his technic for the extirpation of these tumors and the repair of the occasional unsatisfactory result. These things are accomplished in an acceptable fashion.

Dr. Ross presents the accepted and interesting theories on the origin of salivary gland tumors and describes the various types of tumors occurring in such glands. He has included many excellent plates and illustrations on the surgical anatomy of this region with due and particular emphasis on the location of the facial nerve and the precautions to be observed in its handling. He does not hesitate to remove the entire parotid gland for "mixed" tumors, but feels that it is seldom necessary to divide the facial nerve or to remove it with the specimen.

His description of the pathology of these tumors is complete and well illustrated, but probably will not receive due attention from the general surgeon who may be interested simply in the technics of removal. The "sling" operation for the palsy remaining after division of the facial nerve is described, and an evaluation of the various methods of re-establishing the continuity of the nerve after division is given. Dr. Ross includes both the free nerve transplant and anastomosis to the hypoglossal and glosopharyngeal nerves.

This is an excellent reference book on its topic and because of the illustrations will be of some value

to the general surgeon as well as the specialist in maxillofacial surgery.

Veterans Administration Technical Bulletins

Series 10. Volume VII, 1954. 24 pages. Washington, D. C.: Veterans Administration (Department of Medicine and Surgery) 1955.

The subject matter spans wide groups from bulletin to bulletin, but content is good. Covered in this series are such things as dialysis in the treatment of uremia, leprosy, psychotherapy, principles of leptospirosis, bacteremia, coronary atherosclerosis, treatment of arterial hypertension, tumors of the prostate gland, dehydration, electrocardiography and vectorcardiography, and the medical management of patients with incurable cancer. Each subject is authored individually and contributors are all outstanding experts in their fields, most having been borrowed from teaching walks to contribute to this. The bibliographies are consistently excellent.

Comprehensive coverage is given such relatively limited subjects as leprosy, leptospirosis, management of arterial hypertension and others. On more extensive fields such as psychotherapy, electrocardiography and vectorcardiography, a creditable effort touches on significant explanations and major principles without attempt for completeness. The method of presentation of all subjects is uniformly good, there is consistent directness of thought.

The avowed purpose of these bulletins to render available current information on clinical problems as may be encountered among veterans (or for that matter among any patient) is well achieved. This series covers excellently the subjects listed.

Sexual Hygiene and Pathology

By John F. Oliven, M.D., Psychiatrist to Vanderbilt Clinic, Columbia-Presbyterian Medical Center, N. Y. 464 pages. Philadelphia: J. B. Lippincott Company, 1955. Price $10.00.

More and more the physician is facing frank questions by his patients concerning the sexual sphere. From lack of interest or knowledge of the normal and the abnormal, the physician all too often passes on to patients common misconceptions which have grown up over the generations. He should, however, place himself in the position of approaching the physical and mental problems related to sex with the same clinical detachment as with any problem concerning other systems of the body. Surely, however, he has received little or fragmentary instruction on the subject in the medical school, and unless he has made a study of the subject from the physiologic and psychologic aspects, he is very likely to be unprepared to answer the questions which are put to him.

Though this is a book by a psychiatrist, the discussion of the physiologic and physical aspects of sexual matters is adequate and excellent. In the sections of the book dealing with these aspects of the sexual life the author discards many of the beliefs which have been handed down from generation to generation, and even repeated in books on the subject by physicians or psychiatrists for the medical profession.

The psychologic and psychiatric implications of the patient's problems, or questions having to do with sex are discussed in a practical, easily undertsood manner. This subject matter as related to children, to those in the age of puberty and to the adult are discussed in a complete fashion. The discussions dealing with borderline as well as frank abnormalities of a psychiatric nature again are presented in a readable manner.

The author states that he has expressly designed this book for the practicing physician and medical student. He laid the groundwork for this by inquiring from physicians in general practice what problems they encountered in the subject of sex, as well as from those questions which he encountered among his own patients, and from the questions posed by medical students. Feeling these sources offered him a clue as to the needs of the physician and medical student, he wrote this book to answer these needs. As has been indicated before, the book is readable, it does not carry an excess of psychiatric nomenclature and may be highly recommended as a complete and adequate reference book.

Physiology and Pathology of Infant Nutrition

By L. F. Meyer, M.D., and Erich Nassau, M.D., Israel. Translated by Kurt Glaser, M.D., and Susanne Glaser, B.A. Completely revised second edition, 528 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $11.50.

The organization of this volume on infant nutrition is excellent and intriguing. In the first part the physiology of infant nutrition is rather thoroughly discussed. There has been a great need in the past for a text which combines such subjects as development of the healthy infant, the physiology of digestion, absorption of milk and other infant foods and a discussion of both artificial and breast feeding in normal infants with a clinical evaluation of the pathologic disturbances of infant nutrition. Those covered in the present text are not only deficiencies in the specific nutrients but digestive disturbances in infancy and childhood generally.

However the interest achieved by the table of contents of this volume is rather disappointingly frustrating for the American audience because of a lack of incorporation of many advances in infant nutrition and feeding which have been made, largely in this country, in the last ten years. As one example one might point out that there is little mention of evaporated milk. A great many of the therapeutic regimens outlined for the treatment of nutritional deficiency or diarrheal disease seem unfamiliar and based largely upon European experience from the past. The value of these regimens of treatment remains, but, since it is not integrated with some of our present concepts concerning the roles of fat and carbohydrate in nutrition nor with more recent considerations of the role of the electrolyte content of milk mixtures, it would seem to have little appeal to those not already well versed in the subject. Consequently the vast experience of these authors in the treatment of nutritional deficiencies in children is not presented in a fashion that it can be appreciated by the present day student or practitioner.

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Continued from page 925

of medicine at George Washington University School of Medicine, served as a Fellow of the China Medical Board for the study of tropical medicine and parasitology at the University of Puerto Rico Medical School and School of Tropical Medicine.

Dr. Winfred Overholser has been re-elected president of the Washington Institute of Mental Hygiene.

Dr. Reginald S. Lourie, member of the department of psychiatry, Children's Hospital, has been named president-elect of the American Orthopsychiatric Association.

FLORIDA

Dr. Peter J. Spoto, Tarpon Springs, has been appointed clinical director of Anclote Manor.

Dr. Grayson C. Snyder, Blountstown, will serve as chairman of the American Cancer Society's 1956 educational and fund raising drive in Calhoun county.

Dr. Simon D. Doff, Jacksonville, has been elected president of the Florida Trudeau Society. Drs. Howard M. DuBose, Lakeland, and Kip G. Kelso, Vero Beach, will serve as vice-president and secretary respectively.

Dr. George D. Hopkins II, Fort Myers, has been named president of the Lee County Tuberculosis and Health Association. Drs. Merwin E. Buckwald and John S. Stewart, Fort Myers, are members of the Advisory Committee.

Dr. Shaler Richardson, Jacksonville, has been honored as one of the 12 ophthalmologists throughout the nation who will select recipients for the Residency Fellowships in Ophthalmology.

Dr. Benedict R. Harrow, Miami, has been certified as a Diplomate of the American Board of Urology.

Dr. Bernard Tumarkin, Coral Gables, has been certified by the American Board of Psychiatry and Neurology.

Dr. Louise Cason, Miami, has received certification as a Diplomate of the American Board of Pediatrics.

Dr. De Witt C. Daughtry, Miami, has succeeded Dr. R. D. Thompson as Director at Large of the National Tuberculosis Association Board of Directors.

Dr. Francis H. Langley, St. Petersburg, has been installed as president of the Florida Medical Association. The other officers are: Dr. William C. Roberts, Panama City, president-elect; Dr. Meredith Mallory, Orlando, first vice-president; Dr. Kenneth A. Morris, Jacksonville, second vice-president; and Dr. Cecil M. Peek, West Palm Beach, third vice-president. Dr. Samuel M. Day was re-elected secretary-treasurer. Dr. Shaler Richardson will serve his twenty-ninth term as editor of the Association's Journal.

GEORGIA

The Second District Medical Society has elected the following officers: Dr. W. P. Rhyne, Albany, president; Dr. Earl Dupree, Bainbridge, vice-president; and George R. Dillinger, Thomasville, councilor. Dr. Julian B. Neel, Thomasville, was re-elected secretary-treasurer.

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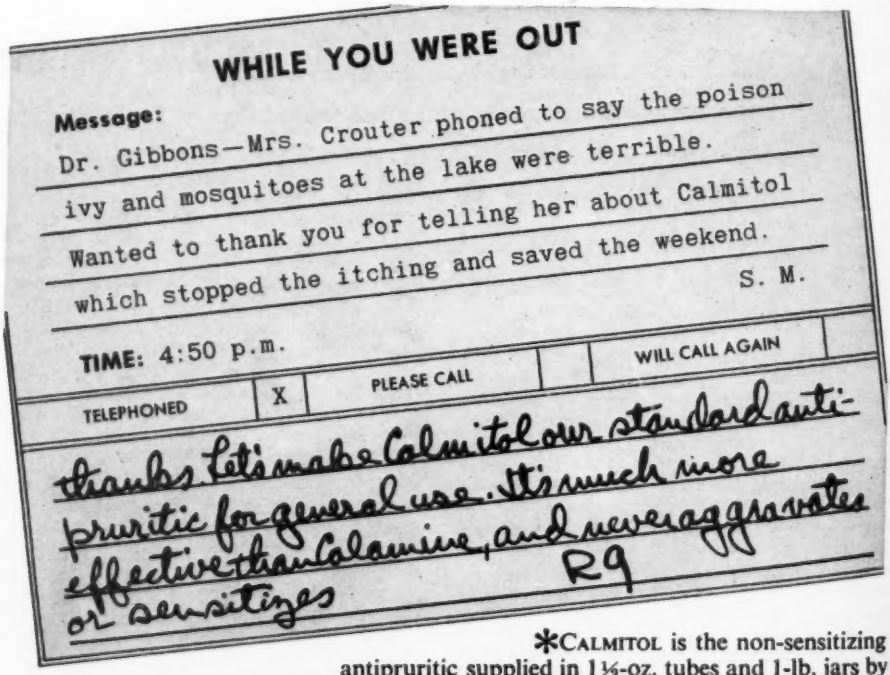
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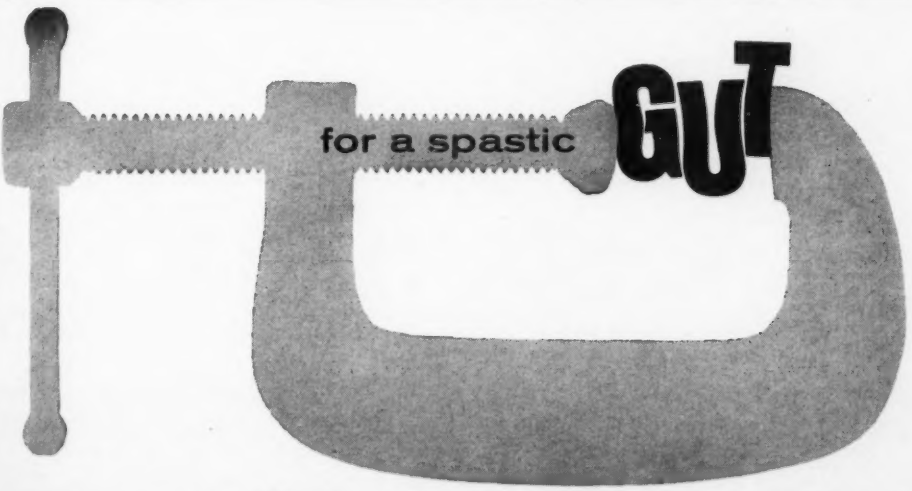

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Continued from page 50

Dr. Grady E. Black, Griffin, has received certification by the American Board of Pediatrics.

The following officers were installed at the meeting of the Seventh District Medical Society: Dr. Ralph Johnson, Rome, president; Dr. G. L. Broaddrick, Dalton, president-elect; and Dr. Cecil B. Elliott, Cedartown, secretary-treasurer.

Dr. Ellison R. Cook III, Savannah, has been appointed director of the newly established Chatham County Clinic for alcoholism.

Dr. W. R. Garner, Gainesville, has been elected president of the Ninth District Medical Society. Dr. George T. Nicholson, Cornelia, is president-elect and Dr. Robert T. Jones II, Canton, will serve as secretary-treasurer.

Dr. C. A. Fleming, Tifton, has assumed the duties of medical officer for the U. S. Air Force radar unit at Tifton.

The officers of the Sixth District Medical Society are: Dr. John Bell, Dublin, president; Dr. Walter Bramblett, Forsyth, vice-president; and Dr. Herbert Olnick, Macon, secretary-treasurer.

Dr. John G. Zirkle, Savannah, has been promoted to colonel in the U. S. Army Reserve.

Drs. L. C. Cheves, Jr., and C. P. Savage, Montezuma, have become associated in the practice of medicine and surgery at the Riverside Sanatorium.

Dr. Edgar Boling, Atlanta, has succeeded Dr. C. Steadman Glisson as president of the Emory Medical Alumni Association. Dr. A. E. Hauck, Atlanta, was re-elected secretary-treasurer.

Dr. F. Phinizy Calhoun, Jr., Atlanta, has been selected as one of 12 ophthalmologists throughout the country who will serve on a committee to select recipients for fellowships in ophthalmology.

Dr. W. M. Barton, Macon, has been named president of the Georgia Society of Ophthalmology and Otolaryngology.

Dr. Ivey Jacobs, Waycross, has become chief of the Ware County Heart Clinic.

Dr. Edwin Leland Brackney, formerly of the University of Minnesota, has been appointed assistant professor of surgery at the Medical College of Georgia.

KENTUCKY

Dr. Francis Massie, Lexington, has been elected president of the Kentucky Surgical Society. Dr. Herman Martin, Ashland, is the new vice-president and Dr. C. Melvin Bernhard, Louisville, is secretary and treasurer.

Dr. R. Arnold Griswold, Louisville, has succeeded Dr. W. Vinson Pierce as president of the Kentucky Chapter of the American College of Surgeons. Dr. J. Farra Van Meter, Lexington, was elected vice-president and Dr. E. C. Strode, also of Lexington, secretary-treasurer.

Continued on page 54

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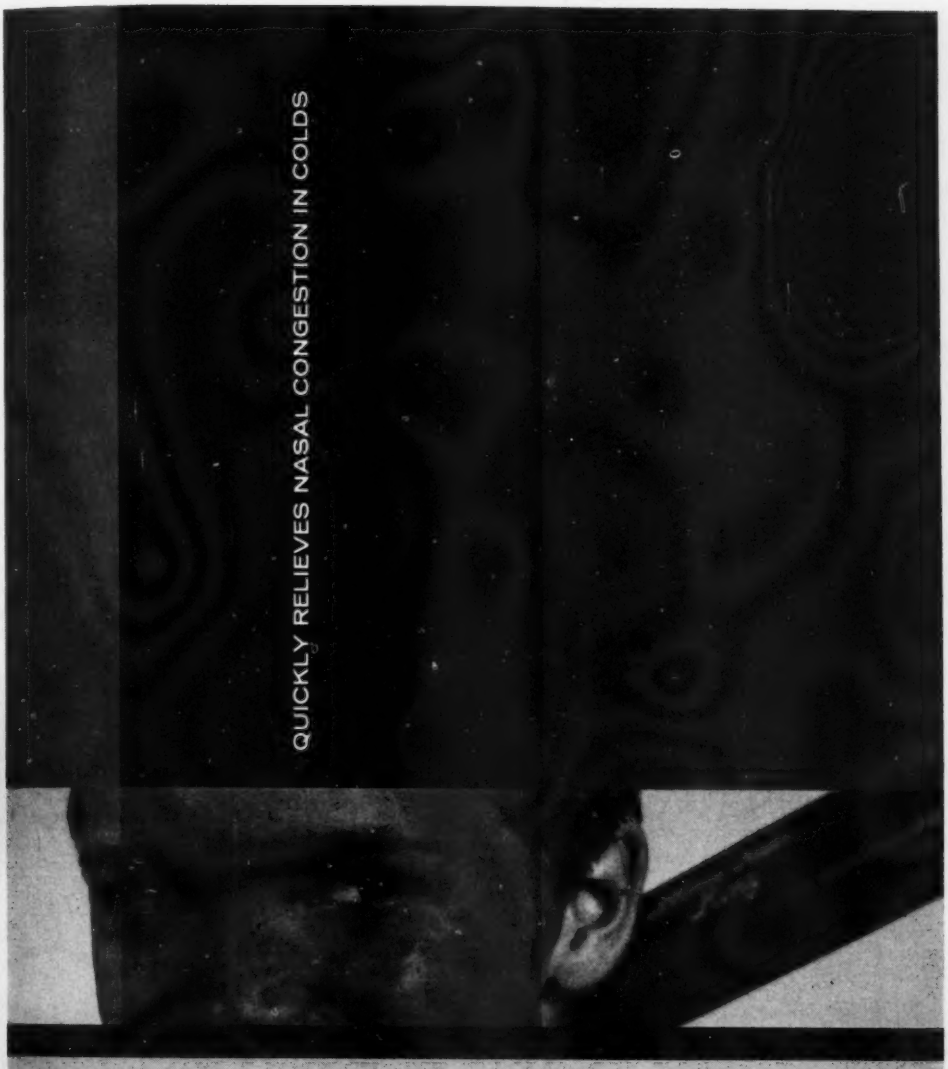

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Continued from page 52

Dr. James T. Gilboy, of the VA Hospital at Dayton, Ohio, has become superintendent of Julius Marks Sanatorium. Dr. Gilboy replaces Dr. Edward J. Murray, who has served as superintendent since 1918. Dr. Murray has resigned because of ill health.

Dr. R. Arnold Griswold, has been re-elected chairman of the board of the Louisville Law-Science Foundation. Dr. David Cox was re-elected treasurer.

Drs. Annie Veech and Alice Pickett, retired Louisville physicians, have received the achievement award of the Alumnae Association of the Woman's College in Philadelphia. Both 1906 graduates of the college, Dr. Pickett retired in 1952 after 25 years as head of the obstetrics department at the University of Louisville School of Medicine; Dr. Veech organized and headed Kentucky's first maternal and child-health program. She served on the City-County Board of Health from 1937 until her resignation in 1949.

Dr. Logan Gragg, Jr., Lexington, has succeeded Dr. Charles Feuss, Jr., as superintendent of Eastern State Hospital.

Dr. Frederick Eberson, former health officer for Henderson, Webster and Union counties, has assumed the duties of director of preventive medicine at the State Health Department.

The American Academy of Pediatrics has named the following Kentucky physicians to membership: Drs. Earl James Farrell, Jr., Newport; Doane Fischer, Harlan; Walter Arnold Kirchner, Louisville; and Hugh Bailey Lynn, Louisville.

Drs. Richard J. Snyder and Eugene Carter, Jr., have joined the staff of the UMW Hospital in Hazard.

Dr. Clifford Best has been appointed to the staff of Hazard Memorial Hospital.

Dr. Benjamin Todd has become associated with the Graves Gilbert Clinic in Bowling Green.

Dr. Etta Wright Best, a pathologist, has joined the staff of the Good Samaritan Hospital in Lexington.

Dr. Leo Kirch is now a member of the staff of the UMW Hospital at Harlan.

LOUISIANA

Dr. Paul D. Abramson, Shreveport, has assumed the presidency of the Louisiana State Medical Society. Those serving with Dr. Abramson are: Dr. H. Ashton Thomas, New Orleans, president-elect; Dr. H. H. Hardy, Jr., Alexandria, first vice-president; Dr. Eugene B. Vickery, New Orleans, second vice-president; and Dr. Eugene St. Martin, Shreveport, third vice-president. Dr. C. Grenes Cole, New Orleans, was re-elected secretary-treasurer.

Dr. Spurgeon M. Wingo, assistant professor of Medicine, at L.S.U. School of Medicine has been named president-elect of the Louisiana Trudeau Society for 1956-1957.

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The Louisiana Dermatological Society has elected Dr. David F. Bradley president and Dr. Raphael Ross, Jr., secretary-treasurer.

Dr. L. H. Strug, clinical professor of surgery at Louisiana State University School of Medicine, will serve as a member of the Executive Committee, Southern Thoracic Surgical Association.

Dr. William W. Frye, dean of the L.S.U. School of Medicine and professor of tropical medicine, has been elected to membership in the American Gastroenterological Association.

Dr. Fred W. Schueler, associate professor of pharmacology at the State University of Iowa, has succeeded Dr. Lawrence Peters as chairman of the department of pharmacology in the Tulane School of Medicine.

Dr. J. M. Perret, Jr., has assumed the duties of president of the New Orleans Pediatric Society. The other officers are: Dr. James Treadway, vice-president and president-elect; Dr. G. L. Fruthaler, secretary; and Dr. Thomas Furlow, treasurer.

Dr. William B. Clark has been elected president of the New Orleans Academy of Ophthalmology. Dr. George L. Hardin is the new vice-president, and Drs. N. C. Farrington and Marie Stanbery will serve as secretary and treasurer respectively.

Dr. John Mackenzie has been named president-elect of the Louisiana Hospital Association.

Dr. Isadore Dyer has been installed as president of the New Orleans Gynecological and Obstetrical Society. Others elected were: Dr. Abe Mickal, president-elect; Dr. Henry Leidenheimer, Jr., vice-president; Dr. C. Gordon Johnson, secretary; and Dr. Daniel W. Goldman, treasurer.

The officers of the Ochsner Foundation Hospital are: Dr. Theodore L. L. Soniat, president; Dr. Patrick H. Hanley, vice-president; and Dr. Harold Horack, secretary.

Dr. J. V. Hopkins, Jr., New Orleans, has assumed the duties of president of the Radiological Society of Louisiana. Dr. W. H. Carroll, Shreveport, is the new vice-president and Dr. W. S. Neal, New Orleans, is secretary-treasurer.

MARYLAND

The Cumberland Memorial Hospital staff officers for 1956 are Dr. Fuller B. Whitworth, president, Dr. Wylie Faw, vice-president, and Dr. Frank T. Cawley, secretary-treasurer.

Dr. H. W. Eliason, Cumberland, has been named to membership on the State Advisory Council on Hospital Construction. Dr. Eliason is chief of pediatrics at the Cumberland Memorial Hospital.

Dr. Robert Eugene Mason, Baltimore, has been elected to fellowship in the American College of Physicians. The following physicians received junior memberships: Drs. William Carl Ebeling, David Grob,

Continued on page 58

"I thought I was getting too old for high heels— low heels didn't help. My leg hurt down to the ankle."
"That's funny. I'm on my feet all day but it was my arms that bothered me."
"My back was so tight I couldn't even get on and off the bus; now I can climb stairs."
"I hope he helps my knee that quick."
Summated, protective corticoid-analgesic therapy
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A single 'Teldrin' *Spansule* capsule taken at bedtime provides *night-long* antihistaminic protection against sleep-hindering nasal stuffiness, sneezing and itching eyes. (Another 'Teldrin' *Spansule* capsule taken on arising helps your patient keep ahead of his hay fever *all day long*.)

This is because Teldrin's unique *sustained release* oral dosage form immediately releases an optimum initial dose of "the most effective of all antihistamines,"[1] chlorprophenpyridamine maleate—then releases a continuous trickle of medication providing an uninterrupted 10 to 12 hour therapeutic effect.

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chlorprophenpyridamine maleate sustained release capsules, S.K.F.

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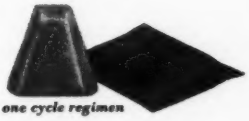
first ⧗ in sustained release oral medication

12 mg. 8 mg.

*T.M. Reg. U.S. Pat. Off. Patent Applied For. 1. Margolin, S., and Tislow, R.: Ann. Allergy *8*:515



one cycle regimen

Vaginal trichomoniasis: lasting cure for 93.8%

Within 72 hours, local irritation no longer troubled this patient. Relief resulted from thorough powder insufflation by her doctor and her use of suppositories at home.

- after clinical study of 48 active cases, Schwartz reported 93.8% were symptom-free in 3 days; 97.9% showed no motile trichomonads on smear in 7 days; 93.8% had no recurrence 1 to 3 months after treatment through one menstrual cycle*
- advantages: contains a specific, trichomonacidal nitrofuran. Kills many secondary invaders but permits Döderlein's bacillus to exist. Effective in blood, pus and vaginal debris
- office treatment: insufflate TRICOFURON Vaginal Powder twice the first week and once a week thereafter
- home treatment: first week—the patient inserts one TRICOFURON Vaginal Suppository each morning and one each night at bedtime. Thereafter: one a day—a second if needed—to maintain trichomonacidal action

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NITROFURANS
a new class of antimicrobials
neither antibiotics nor sulfonamides

VAGINAL SUPPOSITORIES AND POWDER

Suppositories: 0.25% Furoxone® (brand of furazolidone) in a water-miscible base of Carbowax and 20 dendro palmitic acid. Sealed in green foil, box of 12.

Powder: 0.1% Furoxone in an acidic powder base of lactose, dextrose, citric acid and a silicate. Bottle of 30 Gm.

*Schwartz, J.: Obst. Gyn. N. Y. 7:312, 1956.

Digitalis

in its completeness

Each pill is equivalent to one USP Digitalis Unit

Physiologically Standardized therefore always dependable.

Clinical samples sent to physicians upon request.

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Boston, 18, Mass.

Continued from page 55

Richard Starr Ross, all of Baltimore, and Seruch Titus Kimble, Silver Spring.

MISSISSIPPI

Dr. H. C. Ricks has been installed as president of the Mississippi State Medical Association for the coming year. Dr. Howard A. Nelson, a 44-year-old general practitioner from Greenwood, was named president-elect.

The Fifty-Year Club of the State Medical Association has elected the following officers for the new term: Dr. W. H. Frizell, president; Dr. Felix J. Underwood, secretary; and Dr. B. L. Crawford, Tylertown, vice-president.

Dr. W. E. Lotterhos, Jackson, is president of the Mississippi Academy of General Practice. The other officers are: Dr. A. V. Beacham, Magnolia, president-elect; Dr. A. K. McMillan, Lucedale, vice-president; and Dr. A. T. Tatum, Petal, secretary-treasurer.

MISSOURI

Dr. Louis Bernard has been elected president of the St. Louis Urological Society. Dr. Robert Hickey is president-elect and Dr. J. Byron Beare will serve as secretary-treasurer.

Drs. Edward Dempsey, professor of anatomy, James O'Leary, professor of neurology, Irwin Levy, associate professor of neurology, all at Washington University, Sol Sherry, professor of medicine at Jewish Hospital, and Louis Tureen, professor of neurology at St. Louis

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A private hospital for diagnosis and treatment of psychiatric and neurological patients. Hospital and out-patient services.

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DR. HOWARD R. MASTERS
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DR. AMELIA G. WOOD
DR. JAMES ASA SHIELD
DR. GEORGE S. FULTZ, JR.
DR. ROBERT K. WILLIAMS

University, have been appointed to the Medical Advisory Board of the St. Louis Chapter, National Sclerosis Society.

The following St. Louis physicians have been awarded fellowships in the Industrial Medical Foundation: Drs. Bertram L. Bersche, Alvin Henry Diehr, Edwin C. Funsch, William L. Macon, Jr., George H. McDonald, Louis A. Reuter and Raymond C. Sunderman.

Dr. Harry L. Alexander, professor emeritus of the School of Medicine of Washington University, is serving on the National Advisory Allergy and Infectious Diseases Council.

Dr. Bernard Becker, professor of opthalmology and head of the department at Washington University School of Medicine, has been honored as the recipient of the second Lorenzo Holmes Award from the Institute of Medicine of Chicago. Dr. Becker was praised for his work on the pathologic physiology of glaucoma and the relation of adrenal steroids to diabetic vascular disease.

Dr. Raymond O. Muether, associate professor of internal medicine at St. Louis University School of Medicine, has been named president of the staff of the St. Mary's Group of Hospitals of St. Louis University. Dr. Grey Jones, assistant professor of clinical gynecology and obstetrics will serve as vice-president, and Dr. Paul Murphy, associate professor of clinical medicine, and chief of the section of chest diseases has assumed the duties of secretary.

NORTH CAROLINA

Dr. Hamilton W. McKay, past president of the Southern Medical Association and now chairman of the Board of Trustees, recently received two significant citations for his contributions to medicine and the advancement of urology. One citation was presented by Dr. William M. Coppridge from the Southeastern Section of the American Urological Association which cited Dr. McKay for forty years of service in the advancement of urology in the South. He also received the Distinguished Service Award. The Faculty of the School of Medicine of the University of North Carolina cited Dr. McKay for his "high service to medicine and to his fellow man."

Dr. Carl W. Gottschalk, assistant professor of medicine at the University of North Carolina, has been honored as the recipient of the John Horsley Memorial Prize of the University of Virginia.

Dr. Sydenham B. Alexander has been named assistant administrator of the division of health affairs of the University of North Carolina. Dr. Alexander, an associate physician in the University Infirmary for the past seven years, has been clinical assistant professor of medicine since 1953.

OKLAHOMA

Dr. H. M. McClure, Chickasha, has been installed as president of the Oklahoma State Medical Association. The other officers of the Association are: Dr. John F. Burton, Oklahoma City, president-elect; Dr. Forrest Etter, Bartlesville, vice-president; Dr. Wilkie Hoover, Tulsa, delegate to the A.M.A.; Dr. E. H. Shuller, McAlester, alternate delegate; Dr. Clinton Gal-

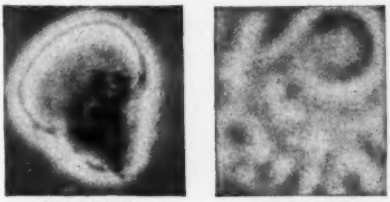
Continued on page 60

HOW VAGISEC LIQUID

EXPLODES

TRICHOMONADS IN 15 SECONDS

WITH the Davis technique, both VAGISEC® liquid and jelly, flare-ups of vaginal trichomoniasis rarely occur. VAGISEC liquid actually *explodes* trichomonads within 15 seconds after douche contact.[1] Better than 90 per cent apparent cures follow use of this new trichomonacide developed as "Carlendacide," by Dr. Carl Henry Davis, noted gynecologist.[2]



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No trichomonad escapes – Three chemicals in VAGISEC liquid combine in balanced blend to weaken the cell membrane, to remove waxes and lipids, and to denature the protein. With its cell wall destroyed, the trichomonad imbibes water, swells and explodes.

The Davis technique† – The physician uses VAGISEC liquid as a vaginal scrub at the office. He prescribes VAGISEC liquid and jelly for concomitant use at home.

Infected husbands re-infect wives[2] – Use of prophylactics breaks the infection cycle.[2] A prescription assures the protection afforded by Schmid quality products – RAMSES,® the finest possible rubber prophylactic; or XXXX (FOUREX)® skins of natural animal membranes, pre-moistened.

References: 1. Davis, C. H.: J.A.M.A. *157*:126 (Jan. 8) 1955. 2. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955.

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Continued from page 59

laher, Shawnee, speaker of the House of Delegates; and Dr. J. Hoyle Carlock, Ardmore, vice-speaker.

Dr. C. E. Northcutt, Ponca City, has been elected to the Board of Directors of the Oklahoma Alcoholism Association.

SOUTH CAROLINA

Dr. T. G. Goldsmith, Greenville, has been elected to the Board of Directors of Association of American Physicians and Surgeons, Inc.

Dr. Bill R. Ewing, formerly of Greenville and Simpsonville, has become associated with Drs. Smith and Ligon on the staff of the Williamston Hospital.

Dr. Sydney Garrett of Six Mile, has joined the staff of the Cannon Memorial Hospital in the general practice of medicine.

TENNESSEE

Dr. John L. Shapiro has been appointed professor and head of the department of pathology at Vanderbilt University School of Medicine. Dr. Shapiro has been acting director of the department since the retirement of Dr. Ernest W. Goodpasture in 1955.

Dr. F. Tom Mitchell, chief of the division of pediatrics at the University of Tennessee, has been honored as a "distinguished alumnus member" of the college's chapter of the national honorary medical society, Alpha Omega Alpha.

Continued on page 64

CITY VIEW
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For the diagnosis and treatment of nervous and mental disorders, and addictions to alcohol and drugs.

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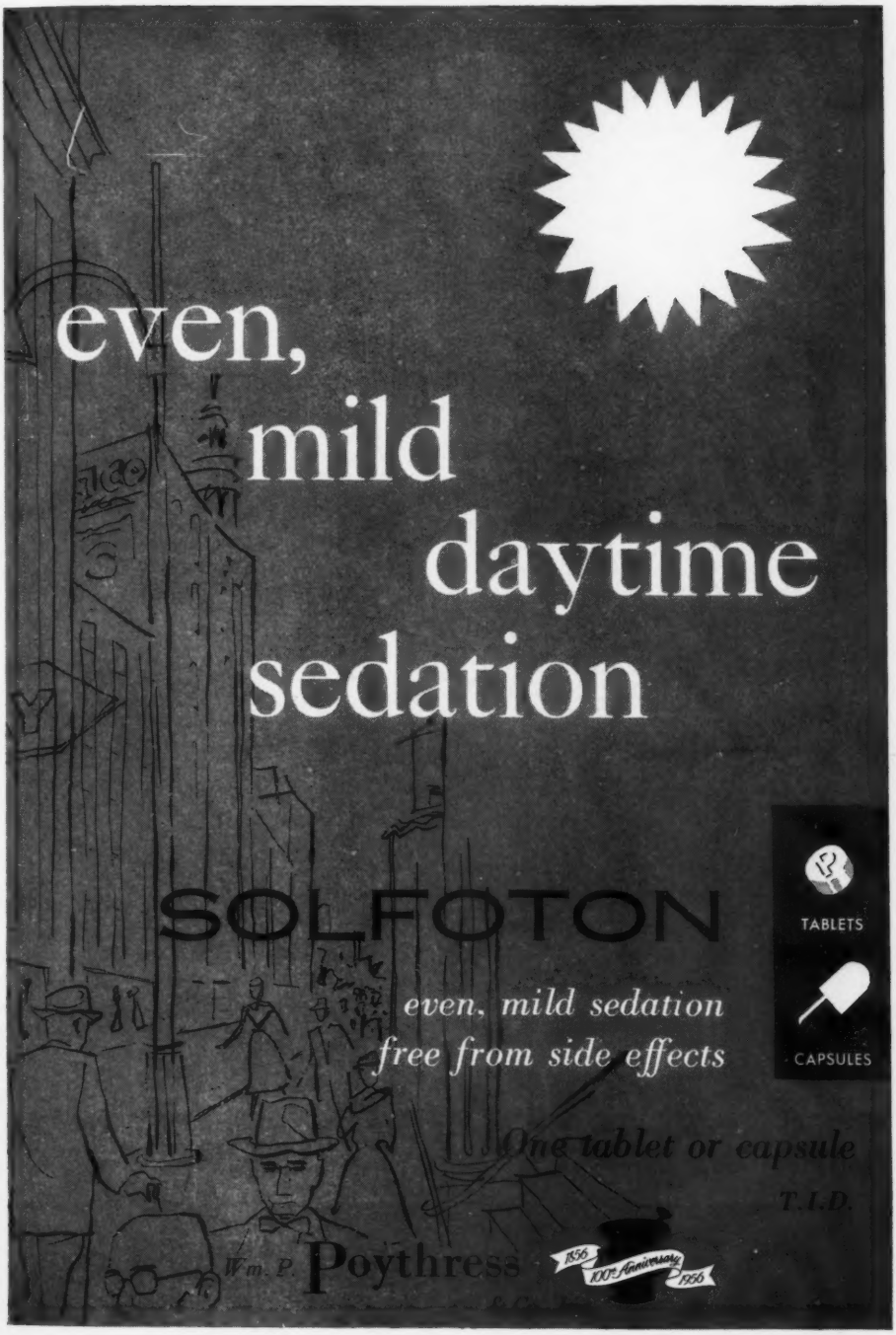
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sedation
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even, mild sedation
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1956

in
persistent
or recurrent
urinary tract
infections
of children...
failure to
treat promptly
and adequately
may produce
serious
sequelae which
can shadow
and shorten
the patient's
life

Average daily dosage for children: 5 to 7 mg. Kg. in 4 divided doses. Tablets: 50 and 100 mg. Oral Suspension: 5 mg. per cc.

"Nitrofurantoin N.N.R. (Furadantin) is an effective urinary antibacterial agent in children."[1]

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"...one of the most effective single agents available at this time."[2]

1. Johnson, S. H., III, and Marshall, M., Jr.: A.M.A. Am. J. Dis. Child. 89:199, 1955. 2. Breakey, R. S.; Holt, S. H., and Siegel, D.: J. Michigan M. Soc. 54:805, 1955.

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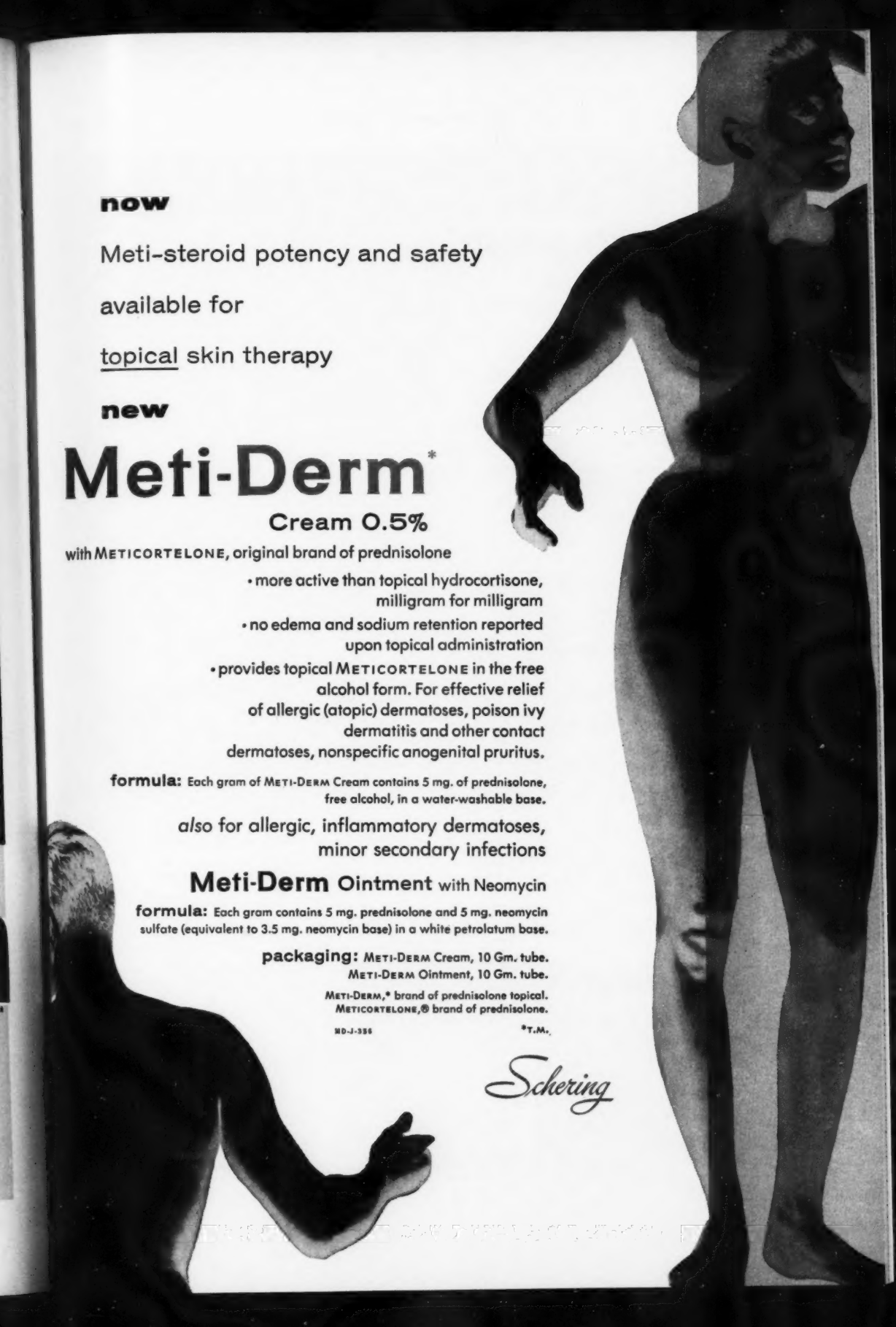
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Meti-steroid potency and safety
available for
topical skin therapy
new
Meti-Derm*
Cream 0.5%
with METICORTELONE, original brand of prednisolone
• more active than topical hydrocortisone, milligram for milligram
• no edema and sodium retention reported upon topical administration
• provides topical METICORTELONE in the free alcohol form. For effective relief of allergic (atopic) dermatoses, poison ivy dermatitis and other contact dermatoses, nonspecific anogenital pruritus.
formula: Each gram of METI-DERM Cream contains 5 mg. of prednisolone, free alcohol, in a water-washable base.
also for allergic, inflammatory dermatoses, minor secondary infections
Meti-Derm Ointment with Neomycin
formula: Each gram contains 5 mg. prednisolone and 5 mg. neomycin sulfate (equivalent to 3.5 mg. neomycin base) in a white petrolatum base.
packaging: METI-DERM Cream, 10 Gm. tube.
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METI-DERM,* brand of prednisolone topical.
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H. D. ALLEN, M.D — DEPARTMENT FOR WOMEN

Terms Reasonable

Continued from page 60

Eight physicians have been appointed assistants on the staff of the University of Tennessee College of Medicine. They are Dr. Paul T. Drenning, division of medicine; Drs. D. H. James, Jr., Charles Walter Brown, and Chris N. Christu, division of pediatrics; Dr. John B. Hamsher, department of urology; Drs. A. H. Crenshaw, Lee W. Milford, Jr., and Rocco A. Calandruccio, department of orthopedic surgery.

Dr. James G. Hughes, professor of pediatrics at the University of Tennessee, has been appointed to the National Council on Infant and Child Care.

TEXAS

Dr. Thomas D. Cronin, Houston, has been elected president of the Texas Society of Plastic Surgeons. Drs. Truman G. Blocker and Steve R. Lewis, both of Galveston, will serve as vice-president and secretary-treasurer respectively.

The new officers of the Texas Chapter, American College of Chest Physicians are Dr. Walter C. Brown, Corpus Christi, president; Dr. John A. Wiggins, Fort Worth, first vice-president; Dr. J. Otis Armstrong, Dallas, second vice-president; and Dr. Lawrence M. Shefts, San Antonio, secretary-treasurer.

Dr. Charles R. Allen, Galveston, has been named president of the Texas Society of Anesthesiologists. Serving with Dr. Allen are Dr. J. D. McCulley, Houston, president-elect; Dr. M. M. Rosenzweig, San An-

Continued on page 66

Westbrook Sanatorium

RICHMOND — Established 1911 — VIRGINIA

A private psychiatric hospital employing modern diagnostic and treatment procedures—electro shock, insulin, psychotherapy, occupational and recreational therapy—for nervous and mental disorders and problems of addiction.

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is the M in **Silmidate-M**

For relief of pain associated with muscle spasm, each tablet of Silmidate-M contains:

500 mg. Mephenesin

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200 mg. Salicylamide

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Dose: 2 to 6 tablets—3 to 5 times daily

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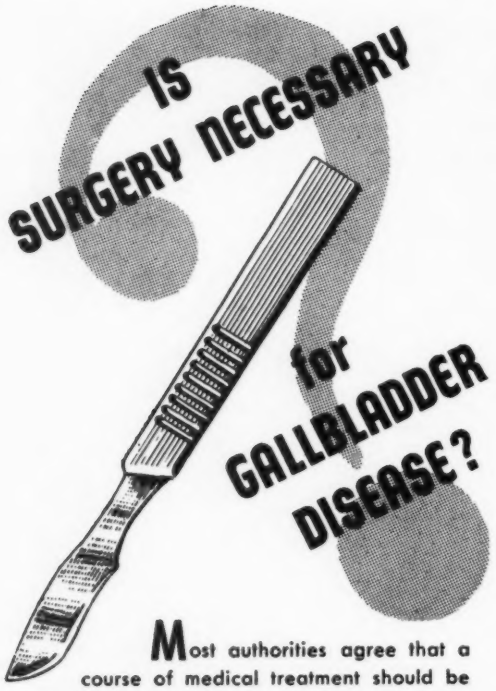

Most authorities agree that a course of medical treatment should be tried before resorting to cholecystectomy This regime includes a low fat diet and use of an effective cholagogue

Many physicians prescribe CHOLOGESTIN, which is both choleretic and cholagogue. It increases the secretion and flow of bile to a remarkable extent, and also liquefies thick and inspissated bile

CHOLOGESTIN

contains salicylated ox bile extract plus pancreatin and sodium bicarbonate. The recommended dosage in the medical treatment of chronic cholecystitis is 1 tablespoonful in cold water after meals

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3 tablets are equivalent to 1 tablespoonful of Chologestin

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DR.....

STREET.....

CITY ..... ZONE..... STATE.....

Continued from page 64

tonio, vice-president; and Dr. Randle J. Brady, Houston, secretary-treasurer.

The Texas Traumatic Surgical Society has selected the following officers: Dr. J. H. Dorman, Dallas, president; Dr. Russell Holt, El Paso, first vice-president; Dr. G. V. Brindley, Jr., Temple, second vice-president; and Dr. W. D. Marrs, Fort Worth, secretary-treasurer.

New officers of the Texas Orthopedic Association for 1956-1957 are Dr. John J. Hinchey, San Antonio, president, and Dr. Lawrence L. Griffin, Austin, vice-president. Dr. Margaret Watkins, Dallas, has been re-elected secretary and treasurer.

Dr. George V. Launey, Jr., Dallas, was elected president of the Texas Chapter, Tulane Alumni Association.

The Past Presidents Association has the following slate of officers for the coming year: Dr. Felix P. Miller, El Paso, president; Dr. G. V. Brindley, Temple, vice-president; and Dr. L. H. Reeves, Fort Worth, secretary.

The 1956-1957 officers of the Texas Dermatological Society are: Dr. Thomas L. Shields, Fort Worth, president; Dr. D. Shelton Blair, Dallas, vice-president; and Dr. E. N. Walsh, Fort Worth, secretary-treasurer.

Dr. George R. Herrmann, Galveston, was recently honored by his former students at the University of Texas Medical Branch. Dr. Herrmann was presented a scroll and plaque in commemoration of his twenty-fifth year as professor of medicine.

Continued on page 68

TULANE UNIVERSITY

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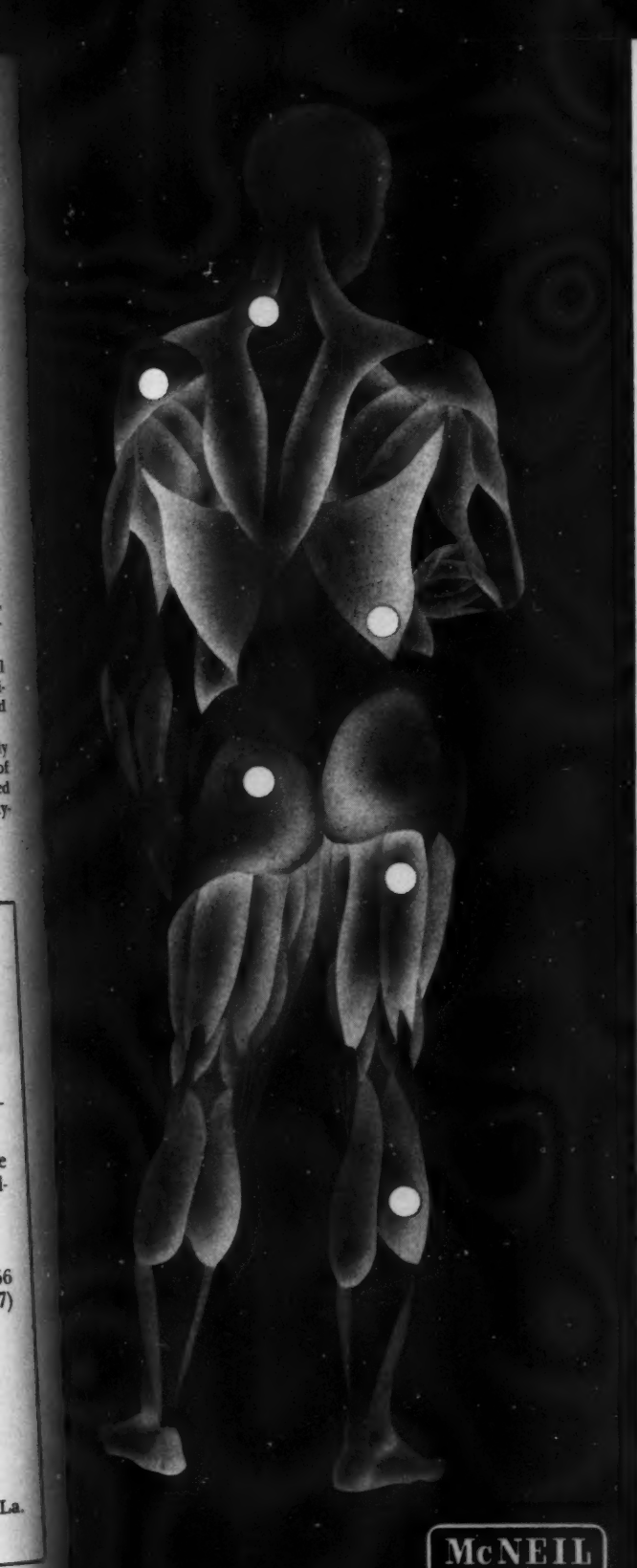

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(Zoxazolamine,† McNeil)

orally effective muscle relaxant

safe: "No irreversible side-effects occurred."[1]

well-tolerated: "The toxic reactions for the most part were easily controlled...."[1]

effective spasmolytic:

"This preliminary report of 100 patients indicates an 85% over-all effectiveness."[1]

Available in yellow scored tablets, 250 mg.

1. Smith, R. T.; Kron, K. M.; Peak, W. P., and Hermann, I. F.: J.A.M.A. 160:745 (Mar. 3) 1956.

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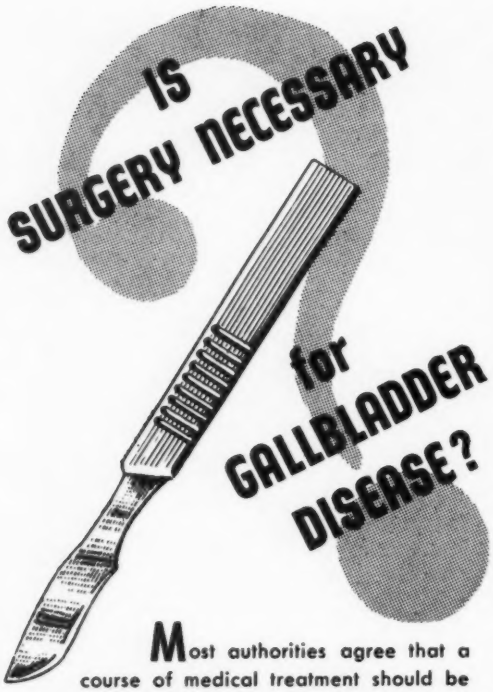

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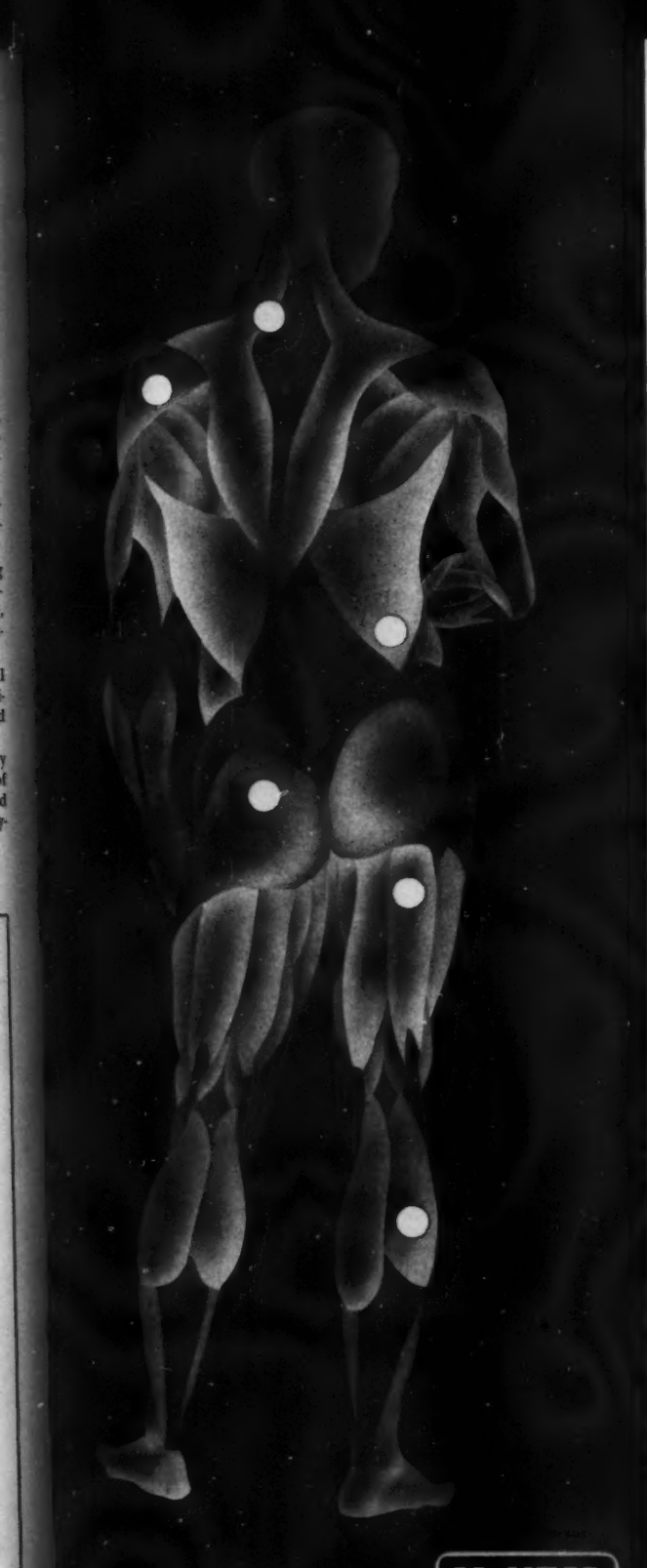

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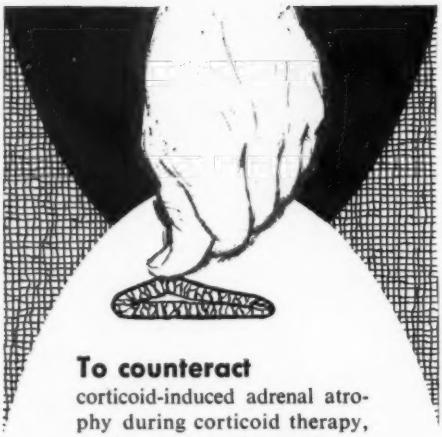

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- When using *prednisone* or *prednisolone:* for every 100 mg. given, inject approximately 100 to 120 units of HP* ACTHAR *Gel.*
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- When using *cortisone:* for every 400 mg. given, inject approximately 100 units of HP*ACTHAR *Gel.*

Discontinue administration of corticoids on the day of the HP*ACTHAR *Gel* injection.

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Continued from page 66

Dr. Charles T. Stone, Sr., professor and chairman of the department of internal medicine at the University of Texas Medical Branch, has been appointed chairman of the medical advisory board of the National Muscular Dystrophy Research Foundation, Inc.

Dr. W. V. Bradshaw, Jr., Fort Worth, has been elected president of the Texas Chapter, American Association of Public Health Physicians. Dr. Roy G. Reed, Victoria, is president-elect and Dr. L. P. Walter, Austin, will serve as vice-president.

The Texas Ophthalmological Association has recently been organized. The officers are Drs. Thomas J. Vanzant, Houston, president; C. Harold Beasley, Fort Worth, vice-president; Louis Daily, Jr., Houston, secretary; and George W. Burch, Tyler, treasurer.

The Alumni Association of the University of Texas Medical Branch will be led by the following officers during the coming year: Drs. L. Bonham Jones, San Antonio, president; John A. Wall, Houston, president-elect; and C. M. Phillips, Levelland, vice-president.

Dr. John L. Otto, Galveston, has been elected president of the Texas Neuropsychiatric Association. The other officers are Dr. Bruce H. Beard, Fort Worth, vice-president; Dr. James Greenwood, Jr., Houston, president-elect; and Dr. Clarence S. Hoeskstra, Dallas, secretary-treasurer.

VIRGINIA

Dr. James P. King, Radford, was appointed by the Governor to membership on a nine-member commission created by the 1956 General Assembly to study the problems of the aging.

Dr. Charles P. Cake, Arlington, has been honored as

Continued on page 73

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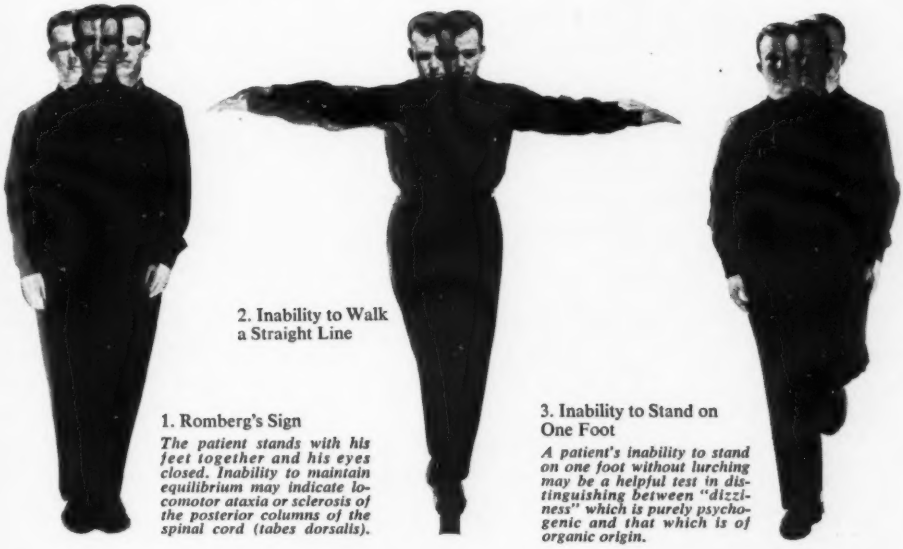
Notes on the Diagnosis and Management of "Dizziness"

II. False Dizziness



1. Romberg's Sign

The patient stands with his feet together and his eyes closed. Inability to maintain equilibrium may indicate locomotor ataxia or sclerosis of the posterior columns of the spinal cord (tabes dorsalis).

2. Inability to Walk a Straight Line

3. Inability to Stand on One Foot

A patient's inability to stand on one foot without lurching may be a helpful test in distinguishing between "dizziness" which is purely psychogenic and that which is of organic origin.

False dizziness is a sensation of sinking or lightheadedness which is often of psychogenic origin. It should be distinguished from true "dizziness" or vertigo[1] in which there is a definite whirling, moving sensation.

Unsteadiness, lightheadedness and similar manifestations of false dizziness[2] may be psychogenic or the result of arteriosclerosis, hypoglycemia, drug sensitivity and general metabolic disturbances such as anemia and malnutrition. Hypertension is often the cause of these symptoms.

Psychogenic dizziness probably originates at the highest brain centers. It may be described as a sense of uncertainty with occasional mild lurching but not to the point of falling. In these patients there is no nausea, no disturbance of vestibular pathways and otologic and neurologic examinations are negative. The sensation is unaffected by head movement. Symptoms usually disappear[3] with complete rest.

Dramamine® has been found highly effective in many of the conditions already mentioned. Maintenance therapy with Dramamine will often keep the patient from becoming incapacitated by his condition.

Dramamine is also a standard for the management of motion sickness and is useful for relief of nausea and vomiting of fenestration procedures and radiation sickness and for relief of "true dizziness" of other disorders.

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1. Swartout, R., III, and Gunther, K.: "Dizziness:" Vertigo and Syncope, GP *8*:35 (Nov.) 1953.

2. DeWeese, D. D.: Symposium: Medical Management of Dizziness. The Importance of Accurate Diagnosis, Tr. Am. Acad. Ophth. *58*:694 (Sept.-Oct.) 1954.

3. Kunkle, E. C.: Central Causes of Vertigo, J. South Carolina M. A. *50*:161 (June) 1954.

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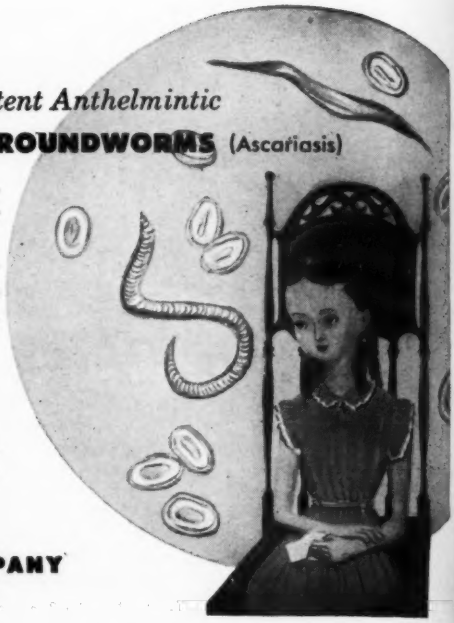

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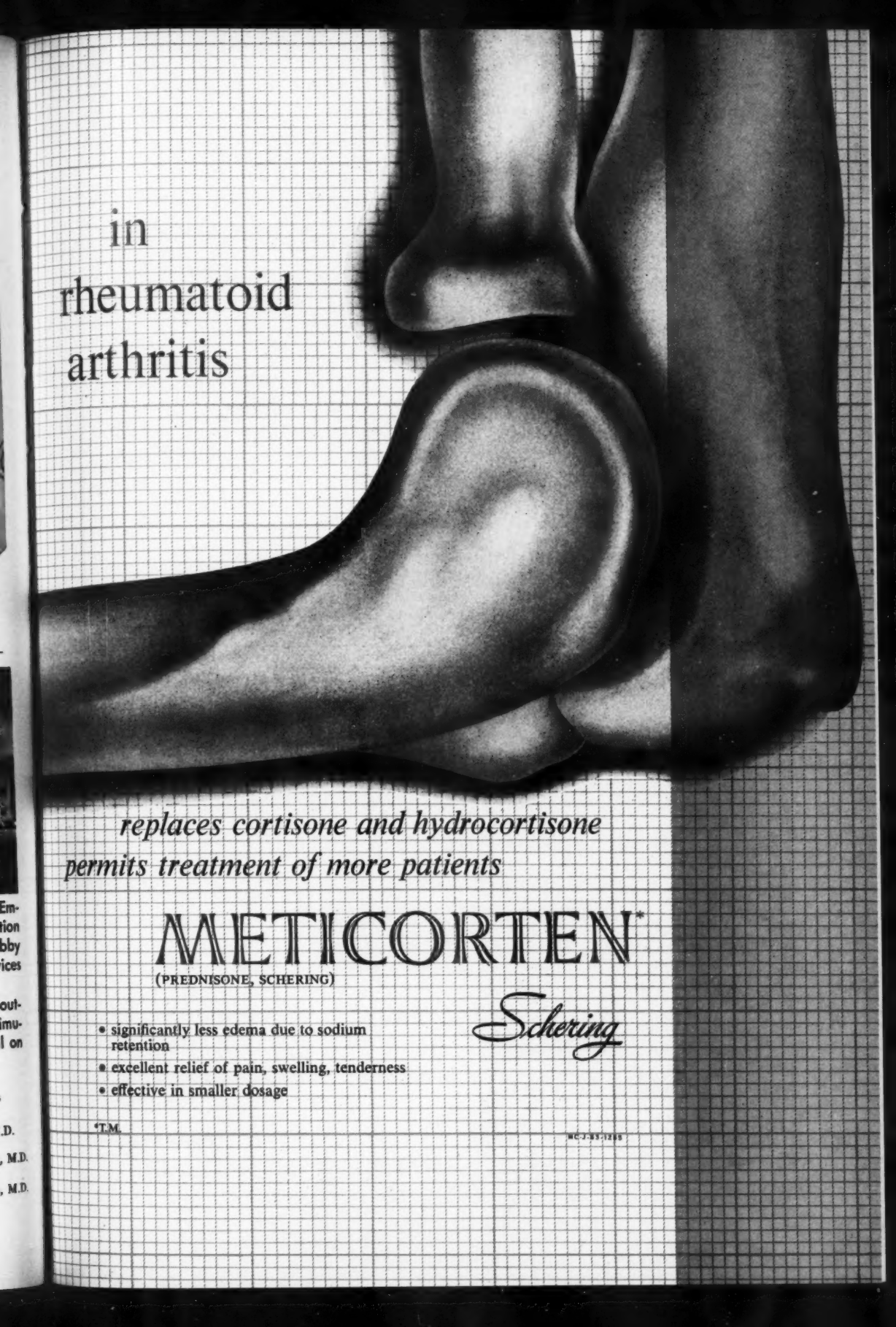

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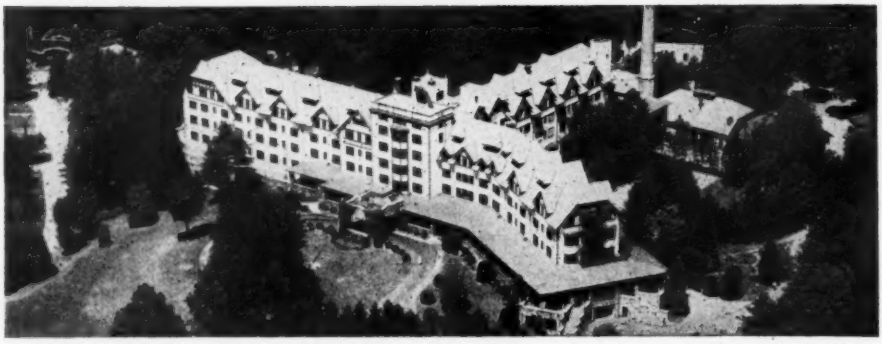

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Continued from page 68

the third recipient of the Douglas Southall Freeman Award. The Virginia Tuberculosis Association makes this award to the person who has contributed the most to the cause of tuberculosis control in the State in the preceding year.

Dr. William H. Barney, Lynchburg, has been named president of the Piedmont Heart Association.

Dr. Maurice M. Bray, Suffolk, has been elected president of the Tidewater Heart Association. Dr. S. L. McDaniel, Norfolk, will serve as one of the vice-presidents.

A portrait of Dr. Thomas Henry Daniel has been unveiled and will hang in the lobby of the Martha Jefferson Hospital, Charlottesville. Dr. Daniel, who has served for many years as chairman of the medical staff of the hospital, spoke briefly at the ceremonies.

Dr. Charles P. Cake, Arlington, has been named president-elect of the Virginia Tuberculosis Association. Dr. Edward S. Ray, Richmond, will serve as second vice-president.

The Virginia Society of Ophthalmology and Otolaryngology has elected the following officers: Dr. Ben Sheppard, Richmond, president; Dr. Emanuel Wallerstein, Richmond, president-elect; Dr. Calvin Burton, Roanoke, vice-president; and Dr. Maynard P. Smith, Richmond, secretary-treasurer. Serving on the executive council are Drs. Peter N. Pastore, G. Slaughter Fitz-Hugh, Howard L. Mitchell, W. Clayton Anderson, Orvin C. Jones, Richard S. Owens, Jr., and Richard O. Smith.

WEST VIRGINIA

Dr. Edward J. Van Liere, dean of West Virginia University School of Medicine, received a high honor recently when he was commissioned to write an artical on hypoxia for the new edition of the Encyclopedia Britanica. Dean Van Liere, one of the world's foremost authorities on hypoxia, has done extensive research in this field and has written two books.

Dr. James W. Lane, Charleston, has been certified by the American Board of Urology.

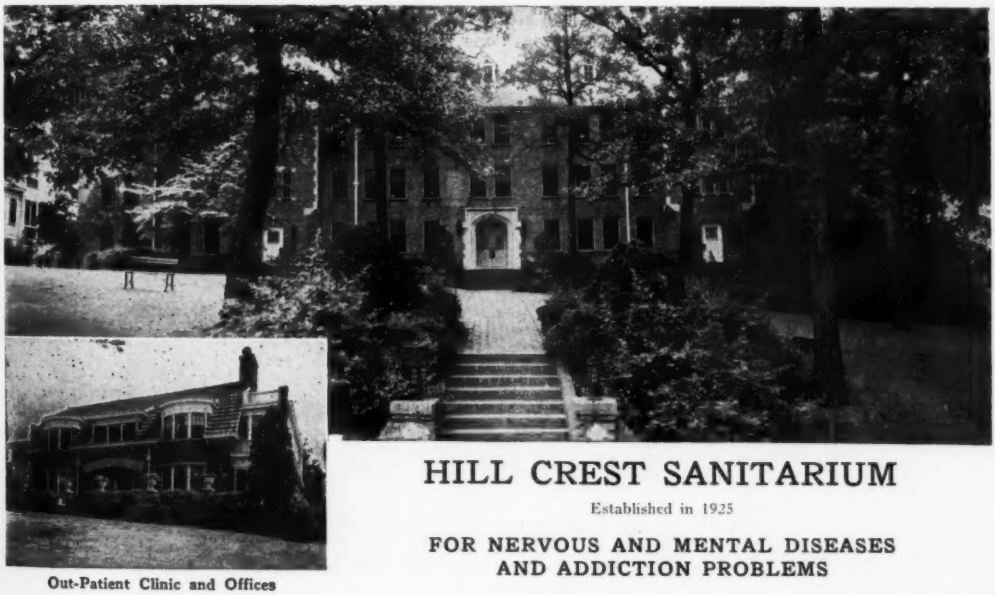
Dr. Grattan G. Irwin, chief of the department of urology at Charleston General Hospital for the past 35 years, has been honored as the recipient of an engraved plaque in recognition of his services to the profession and the community. The award was made following a series of special lectures at the Hospital.

Dr. George F. Fordham, Mullens, has been elected to fellowship in the Industrial Medical Association.

Dr. Wheeler Russel Gregory, Jackson, Louisiana, has succeeded Dr. Ralph Zemer as superintendent of the West Virginia Training School at St. Marys.

Dr. William R. Laird, surgeon at the Laird Memorial Hospital and president of the Laird Foundation, received the honorary degree of Doctor of Literature at the Medical College of Virginia.

Dr. George M. Lyon, manager of the Veterans Administration hospital at Huntington, has been awarded an honorary Doctor of Science degree from Denison University at Granville, Ohio.



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